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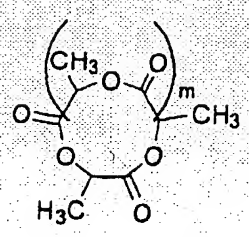
(54) PROCESS FOR THE PREPARATION OF CYCLIC LACTIC ACID OLIGOMERS

(57) The object of the present invention is to provide a novel method for effectively producing a cyclic lactic acid oligomer, and a cyclic lactic acid oligomer produced by the method. According to the present invention, there is provided a method for producing a cyclic lactic acid oligomer represented by the following formula (1):



(1)

wherein m represents an integer of 1 to 30,
wherein lactides are polymerized in the presence of an alkali metal compound represented by the following formula (2):

R-Y-Me (2)

wherein

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R represents an aliphatic group, aromatic group, $-Si(R^{10})(R^{11})(R^{12})$, $-CH(R^{20})CONR^{21}R^{22}$ or $-CH(R^{30})COOR^{31}$, wherein each of R^{10}, R^{11} and R^{12} independently represents an aliphatic or aromatic group, R^{20} represents an aliphatic group, each of R^{21} and R^{22} independently represents a hydrogen atom, aliphatic group or aromatic group, R^{30} represents an aliphatic group, and R^{31} represents a hydrogen atom, aliphatic group or aromatic group;
Y represents -O-, -S- or $-NR^{40}-$, wherein R^{40} represents a hydrogen atom, aliphatic group or aromatic group; and
Me represents an alkali metal; and,
a cyclic lactic acid oligomer produced by the above production method.

Description

TECHNICAL FIELD

[0001] The present invention relates to a method for producing a cyclic lactic acid oligomer, and a cyclic lactic acid oligomer produced by the production method.

BACKGROUND ART

[0002] A lactic acid oligomer having a cyclic structure is a useful compound which is used as a medicament such as a tumor cell growth inhibiting agent (Japanese Patent Application Laying-Open (Kokai) No. 3-193731) or an antineoplastic agent (Japanese Patent Application Laying-Open (Kokai) No. 9-227388), or an intermediate thereof.

[0003] The conventional method for producing such a lactic acid oligomer involves subjecting lactic acids to dehydration condensation by heating under an inactive atmosphere, and then separating and collecting an oligomer component from the obtained reaction products.

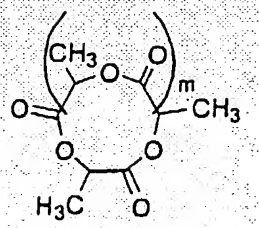
[0004] However, since it is difficult to produce a lactic acid oligomer selectively by this conventional method and that the lactic acid polymer obtained in the dehydration condensation process of lactic acids has a broad molecular weight distribution, containing high polymers, it is necessary to separate and collect a lactic acid oligomer by separation means such as chromatography.

DISCLOSURE OF THE INVENTION

[0005] The object of the present invention is to provide a novel method for effectively producing a cyclic lactic acid oligomer, and a cyclic lactic acid oligomer produced by the method.

[0006] As a result of concentrated research to achieve the aforementioned object, the present inventors have found that a cyclic lactic acid oligomer can be produced effectively by polymerization of lactides in the presence of a certain alkali metal compound, thereby providing the present invention.

[0007] Thus, according to the present invention, there is provided a method for producing a cyclic lactic acid oligomer represented by the following formula (1):



(1)

wherein m represents an integer of 1 to 30,
wherein lactides are polymerized in the presence of an alkali metal compound represented by the following formula (2):

R-Y-Me (2)

wherein

R represents an aliphatic group, aromatic group, $-Si(R^{10})(R^{11})(R^{12})$, $-CH(R^{20})CONR^{21}R^{22}$ or $-CH(R^{30})COOR^{31}$, wherein each of R^{10}, R^{11} and R^{12} independently represents an aliphatic or aromatic group, R^{20} represents an aliphatic group, each of R^{21} and R^{22} independently represents a hydrogen atom, aliphatic group or aromatic group, R^{30} represents an aliphatic group, and R^{31} represents a hydrogen atom, aliphatic group or aromatic group;
Y represents -O-, -S- or $-NR^{40}-$, wherein R^{40} represents a hydrogen atom, aliphatic group or aromatic group; and
Me represents an alkali metal.

[0008] Preferably, the alkali metal compound is a compound of formula (2) wherein R represents an alkyl group having 1 to 12 carbon atoms, aryl group having 6 to 30 carbon atoms, $-Si(R^{10})(R^{11})(R^{12})$, $-CH(R^{20})CONR^{21}R^{22}$ or -CH

$(R^{30})COOR^{31}$, wherein each of R^{10}, R^{11} and R^{12} independently represents an aliphatic or aromatic group, R^{20} represents an aliphatic group, each of R^{21} and R^{22} independently represents a hydrogen atom, aliphatic group or aromatic group, R^{30} represents an aliphatic group, and R^{31} represents a hydrogen atom, aliphatic group or aromatic group.

[0009] Preferably, the alkali metal compound is a compound of formula (2) wherein Y is -O- or -S-.

[0010] Preferably, the alkali metal compound is a compound of formula (2) wherein Me is lithium.

[0011] Preferably, in formula (1), m is an integer of 1 to 21.

[0012] According to one embodiment of the present invention, as the alkali metal compound, there is used any of: a compound of formula (2) wherein R is an aliphatic group having 4 or more carbon atoms; a compound of formula (2) wherein R is an aromatic group and Y is -S-; or a compound of formula (2) wherein R is $-CH(R^{20})CONR^{21}R^{22}$ wherein R^{20} represents an aliphatic group and each of R^{21} and R^{22} independently represents a hydrogen atom, aliphatic group or aromatic group. In the case of using such alkali metal compounds, cyclic lactic acid oligomer is selectively produced substantially free of chain lactic acid oligomer.

[0013] According to another aspect of the present invention, there is provided a cyclic lactic acid oligomer, which is produced by the aforementioned method for producing a cyclic lactic acid oligomer according to the present invention. Preferably, there is provided the cyclic lactic acid oligomer which is substantially free of chain lactic acid oligomer.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014]

Figure 1 shows a general view of NMR of the product obtained in Example 1.
Figure 2 shows a partial scale view of NMR of Figure 1.
Figure 3 shows a partial scale view of NMR of Figure 1.
Figure 4 shows a general view of NMR of the product obtained in Example 2.
Figure 5 shows a partial scale view of NMR of Figure 4.
Figure 6 shows a partial scale view of NMR of Figure 4.
Figure 7 shows a general view of NMR of the product obtained in Example 3.
Figure 8 shows a partial scale view of NMR of Figure 7.
Figure 9 shows a partial scale view of NMR of Figure 7.
Figure 10 shows an MS spectrum of the product obtained in Example 4.
Figure 11 shows a general view of NMR of the product obtained in Example 4.
Figure 12 shows a partial scale view of NMR of Figure 11.
Figure 13 shows a partial scale view of NMR of Figure 11.
Figure 14 shows a general view of NMR of the product obtained in Example 5.
Figure 15 shows a partial scale view of NMR of Figure 14.
Figure 16 shows a partial scale view of NMR of Figure 14.
Figure 17 shows a general view of NMR of the product obtained in Example 6.
Figure 18 shows a partial scale view of NMR of Figure 17.
Figure 19 shows a partial scale view of NMR of Figure 17.
Figure 20 shows a general view of NMR of the product obtained in Example 7.
Figure 21 shows a partial scale view of NMR of Figure 20.
Figure 22 shows a partial scale view of NMR of Figure 20.
Figure 23 shows a general view of NMR of the product obtained in Example 8.
Figure 24 shows a partial scale view of NMR of Figure 23.
Figure 25 shows a partial scale view of NMR of Figure 23.
Figure 26 shows a general view of NMR of the product obtained in Example 9.
Figure 27 shows a partial scale view of NMR of Figure 26.
Figure 28 shows an MS spectrum of the product obtained in Example 10.
Figure 29 shows a general view of NMR of the product obtained in Example 10.
Figure 30 shows a partial scale view of NMR of Figure 29.
Figure 31 shows a partial scale view of NMR of Figure 29.

THE BEST MODE FOR CARRYING OUT THE INVENTION

[0015] The embodiments and methods for carrying out the present invention are described in detail below.

[0016] The method for producing a cyclic lactic acid oligomer of the present invention is characterized in that lactides are polymerized in the presence of an alkali metal compound represented by the following formula (2):

R-Y-Me (2)

wherein

R represents an aliphatic group, aromatic group, -Si(R^{10})(R^{11})(R^{12}), -CH(R^{20}) $CONR^{21}R^{22}$ or -CH(R^{30})$COOR^{31}$, wherein each of R^{10}, R^{11} and R^{12} independently represents an aliphatic or aromatic group, R^{20} represents an aliphatic group, each of R^{21} and R^{22} independently represents a hydrogen atom, aliphatic group or aromatic group, R^{30} represents an aliphatic group, and R^{31} represents a hydrogen atom, aliphatic group or aromatic group;
Y represents -O-, -S- or -NR^{40}-, wherein R^{40} represents a hydrogen atom, aliphatic group or aromatic group; and
Me represents an alkali metal.

[0017] The raw material in the production method of the present invention is lactide (3,6-dimethyl-1,4-dioxane-2,5-dione) obtained by condensation of two molecules of lactic acid by dehydration, and this lactide is reacted in the presence of the alkali metal compound represented by the above-mentioned formula (2). The formula (2):

R-Y-Me (2)

is described below.

[0018] In formula (2), R represents an aliphatic group, aromatic group, -Si(R^{10})(R^{11})(R^{12}), -CH(R^{20}) $CONR^{21}R^{22}$ or -CH(R^{30})$COOR^{31}$, wherein each of R^{10}, R^{11} and R^{12} independently represents an aliphatic or aromatic group, R^{20} represents an aliphatic group, each of R^{21} and R^{22} independently represents a hydrogen atom, aliphatic group or aromatic group, R^{30} represents an aliphatic group, and R^{31} represents a hydrogen atom, aliphatic group or aromatic group.

[0019] The aliphatic group in the present specification may be a straight chain, branched chain, cyclic, or combined thereof, and may be saturated or unsaturated aliphatic hydrocarbon group having 1 to 12, preferably 1 to 6 carbon atoms. Examples thereof include alkyl groups such as methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, octyl and dodecyl, and cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclooctyl and cyclododecyl. The aliphatic group may be an unsaturated hydrocarbon group having a double or triple bond.

[0020] The aromatic group in the present invention may be an aryl group and an arylalkyl group having 6 to 30, preferably 6 to 20, more preferably 6 to 12, and further more preferably 6 to 10 carbon atoms. Examples of the aryl group include phenyl, tolyl and naphthyl, and examples of the arylalkyl group include benzyl, phenethyl and naphthylmethyl.

[0021] The aliphatic group and the aromatic group may have one or more substituent(s). The type of substituents is not particularly limited, and examples include a straight chain, branched chain or cyclic alkyl group, a straight chain, branched chain or cyclic alkenyl group, a straight chain, branched chain or cyclic alkynyl group, an aryl group, an acyloxy group, an alkoxycarbonyloxy group, an aryloxycarbonyloxy group, a carbamoyloxy group, a carbonamide group, a sulfonamide group, a carbamoyl group, a sulfamoyl group, an alkoxy group, an aryloxy group, an aryloxycarbonyl group, an alkoxycarbonyl group, an N-acylsulfamoyl group, an N-sulfamoylcarbamoyl group, an alkylsulfonyl group, an arylsulfonyl group, an alkoxycarbonylamino group, an aryloxycarbonylamino group, an amino group, an ammonio group, a cyano group, a nitro group, a carboxyl group, a hydroxyl group, a sulfo group, a mercapto group, an alkylsulfinyl group, an arylsulfinyl group, an alkylthio group, an arylthio group, an ureide group, a heterocyclic group (e.g. a monocyclic or condensed ring containing at least one or more nitrogen, oxygen or sulfur atom(s) and consisting of 3 to 12 ring forming members), a heterocyclic oxy group, a heterocyclic thio group, an acyl group, a sulfamoylamino group, a silyl group, and a halogen atom. In the above description, the carbon number of alkyl, alkenyl, alkynyl and alkoxy is generally 1 to 12, preferably 1 to 6, and the carbon number of aryl is generally 6 to 20, preferably 6 to 10.

[0022] In formula (2), Y represents -O-, -S- or -NR^{40}-, wherein R^{40} represents a hydrogen atom, aliphatic group or aromatic group. Preferably, Y is -O- or -S-. Examples of aliphatic or aromatic groups represented by R^{40} are as stated above.

[0023] In formula (2), Me represents an alkali metal. Examples of alkali metal include Li, Na or K, and Li is preferable.

[0024] Among compounds represented by formula (2), the compounds having asymmetric carbon atoms may be any one of (R) form, (S) form, and (R),(S) form.

[0025] A method for obtaining an alkali metal compound represented by formula (2) is not particularly limited, and a person skilled in the art can obtain the compound as appropriate. For example, the alkali metal compound can be obtained by reaction of R-YH with an alkylated alkali metal such as n-butyllithium.

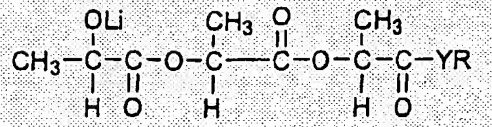
[0026] Where lactides are polymerized in the presence of an alkali metal compound represented by formula (2) according to the method of the present invention, the amount of alkali metal compound (R-Y-Me) is preferably 0.1 to

1 mole, more preferably 0.2 to 0.3 mole per mole of lactide.

[0027] When the method of the present invention is carried out, the reaction temperature is not particularly limited as long as the reaction progresses, and the reaction temperature is preferably -100°C to room temperature, more preferably -78°C to -50°C. It is preferable that the reaction is initiated at a temperature of -78°C to -50°C and that the reaction is performed while gradually raising the temperature to room temperature.

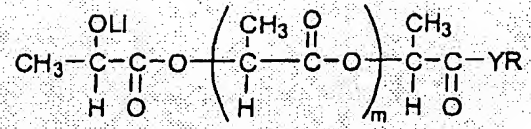
[0028] Polymerization reaction of lactides in the method of the present invention is preferably carried out in the presence of a reaction solvent. The reaction solvent is not particularly limited as long as it is inactive for the reaction, and examples of preferred solvents include cyclic ether such as tetrahydrofuran, diethylether, and dimethoxyethane. Examples of reaction atmospheres may be inactive gas atmospheres such as nitrogen gas and argon gas. Reaction pressure is not particularly limited, and is preferably normal pressure.

[0029] Next, the reaction mechanism of production of a cyclic lactic acid oligomer by the method of the present invention is described, but the following theory is not intended to limit the scope of the present invention. The case of using Li as an alkali metal compound is described herein, but it is considered that the reaction mechanism is similar where other alkali metal compounds such as Na or K are used. In the polymerization reaction of lactides in the method of the present invention, first, a lithium compound and lactide are reacted to generate a chain lactic acid derivative represented by the following formula (4):



(4)

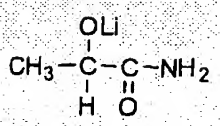
wherein Y and R are as defined above in the present specification. Then, lactide is reacted with this compound to generate a chain lactic acid oligomer represented by the following formula (5):



(5)

wherein m, Y and R are as defined above in the present specification. Subsequently, RYLi is removed from this compound, and the compound is cyclized, so that a cyclic lactic acid oligomer of the above formula (1) is considered to be generated.

[0030] The composition of a lactic acid oligomer obtained by the method of the present invention is changed depending on an alkali metal compound used as a reaction assistant. For example where the alkali metal compound (preferably a lithium compound) of alkyl alcohol having 1 to 3 carbon atoms is used, a mixture (the ratio of cyclic lactic acid oligomer : 80 to 85% by weight) of a cyclic lactic acid oligomer and a chain oligomer can be obtained. In contrast, where the alkali metal compound of alkyl alcohol having 4 or more carbon atoms such as t-butyl alcohol, or the alkali metal compound of. thiophenol and the like, is used, substantially only cyclic lactic acid oligomer can be obtained selectively. Also, substantially only cyclic lactic acid oligomer can be obtained selectively by using, as an alkali metal compound, a compound of formula (2) wherein R is -CH(R^{20}) $CONR^{21}R^{22}$, wherein R^{20} is an aliphatic group and each of R^{21} and R^{22} is independently a hydrogen atom, aliphatic group or an aromatic group, more specifically, for example, lactic acid amide represented by the following formula (3):



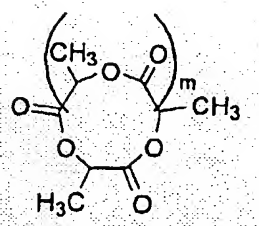
(3)

The term "substantially only cyclic lactic acid oligomer is obtained selectively" is used in the present specification to

mean that substantially no chain lactic acid oligomers are generated in a reaction product, and specifically it means that the ratio of chain lactic acid oligomer to total lactic acid oligomer in a reaction product is generally 10% by weight or less, preferably 5% by weight or less, and particularly preferably 3% by weight or less.

[0031] As stated above, one advantage of the present invention is that the composition of a cyclic lactic acid oligomer and a chain oligomer in a reaction product can be controlled by selection of the type of an alkali metal compound.

[0032] According to the method of the present invention, there is produced a cyclic lactic acid oligomer represented by the following formula (1):



(1)

[0033] In formula (1), m represents an integer of 1 to 30, preferably 1 to 21.

[0034] The reaction product obtained by the method of the present invention is generally a mixture of cyclic lactic acid oligomers, wherein m represents an integer of 1 to 30, for example, 1 to 28, 1 to 25, 1 to 21, or 1 to 19.

[0035] The present invention also relates to a cyclic lactic acid oligomer, which is produced by the aforementioned method for producing a cyclic lactic acid oligomer of the present invention. In a preferred embodiment for the present invention, a mixture of cyclic lactic acid oligomers substantially free of chain lactic acid oligomers can be produced.

[0036] The mixture of cyclic lactic acid oligomers produced by the method of the present invention (or a single substance obtained by purification from the mixture) is useful as a tumor cell growth inhibiting agent, an antineoplastic agent, a preventive agent against cancer metastasis, a QOL improving agent for cancer patients, an immune activating agent, and the like, and the mixture can also be used for prevention and/or treatment of diabetes or diabetes complications since it has an action of reducing blood sugar level. Moreover, the mixture of cyclic lactic acid oligomers produced by the method of the present invention (or a single substance obtained by purification from the mixture) has an action of repressing excessive appetite and promoting basal metabolism, and so it can be used also as a medicament useful for improvement and/or prevention of adiposis and enhancement of effects of kinesitherapy, and is also useful as an agent for promoting glycogen accumulation or an agent for enhancing physical fitness. Furthermore, a cyclic lactic acid oligomer produced by the method of the present invention is useful not only as a medicament, but also as health foods or diet supplements including beverages, which is generally called soft drinks, drinkable preparations, health foods, specific hygienic foods, functional foods, function activating foods, nutritional supplementary foods, supplements, feed, feed additives, and the like.

[0037] The present invention is further described in the following examples. It is apparent to those skilled in the art that materials, usage, proportion, treatment, treatment process and the like shown in the following examples can be modified as appropriate, as long as the modifications are within the spirit and scope of the invention, and the examples are not intended to limit the scope of the invention.

EXAMPLES

Example 1

[0038] A THF solution (2ml) in which 0.033g (1.03mmol) of methanol was dissolved was added to a 50ml double-cap eggplant-shaped flask under a nitrogen atmosphere, and cooled to -78°C in a dry ice/acetone bath. Then, 0.64ml (1.00mmol) of n-butyllithium was added thereto and the mixture was stirred for 15 minutes. Further, a THF solution (2ml) in which 0.576g (4.00mmol) of (3R,6R)-(+)-3,6-dimethyl-1,4-dioxane-2,5-dione was dissolved was added thereto and stirred, and the temperature was gradually raised to room temperature over 4 hours.

[0039] After completion of stirring, 2ml of saturated ammonium chloride was added to the mixture while maintaining a nitrogen atmosphere, and 10ml of water was further added thereto. The mixture was extracted with chloroform and a saturated saline solution and washed, and then anhydrous sodium sulfate was added thereto and dried overnight. The obtained product was subjected to vacuum concentration in which solvent was completely removed with a vacuum pump. As a result, 0.551g (yield 90.5%) of product consisting of a mixture of cyclic oligo-lactate and chain oligo-lactate was obtained with a weight ratio between cyclic oligomer and chain oligomer being 84 : 16.

[0040] A general view of NMR of the product obtained in Example 1 is shown in Figure 1, and scale views of a part of Figure 1 are shown in Figures 2 and 3.

Example 2

[0041] A THF solution (2ml) in which 0.054g (1.17mmol) of ethanol was dissolved was added to a 50ml double-cap eggplant-shaped flask under a nitrogen atmosphere, and cooled to -78°C in a dry ice/acetone bath. Then, 0.64ml (1.00mmol) of n-butyllithium was added thereto and the mixture was stirred for 15 minutes. Further, a THF solution (2ml) in which 0.576g (4.00mmol) of (3R,6R)-(+)-3,6-dimethyl-1,4-dioxane-2,5-dione was dissolved was added thereto and stirred for 30 minutes.

[0042] After completion of stirring, 2ml of saturated ammonium chloride was added to the mixture while maintaining a nitrogen atmosphere and 10ml of water was further added thereto, and then the temperature was raised to room temperature by removal of the dry ice/acetone bath. Subsequently, the mixture was extracted with 20ml of ether 8 times, and the ether layer was washed with 30ml of saturated saline solution. Then, anhydrous sodium sulfate was added thereto and dried while stirring for 1 hour. The obtained product was subjected to vacuum concentration in which solvent was completely removed with a vacuum pump. As a result, 0.535g (yield 84.9%) of product consisting of a mixture of cyclic oligo-lactate and chain oligo-lactate was obtained with a weight ratio between cyclic oligomer and chain oligomer being 82:18.

[0043] A general view of NMR of the product obtained in Example 2 is shown in Figure 4 and scale views of a part of Figure 4 are shown in Figures 5 and 6.

Example 3

[0044] A THF solution (2ml) in which 0.062g (1.03mmol) of 2-propanol was dissolved was added to a 50ml double-cap eggplant-shaped flask under a nitrogen atmosphere, and cooled to -78°C in a dry ice/acetone bath. Then, 0.64ml (1.00mmol) of n-butyllithium was added thereto and the mixture was stirred for 15 minutes. Further, a THF solution (2ml) in which 0.576g (4.00mmol) of (3R,6R)-(+)-3,6-dimethyl-1,4-dioxane-2,5-dione was dissolved was added thereto and stirred , and the temperature was gradually raised to room temperature over 4 hours.

[0045] After completion of stirring, 2ml of saturated ammonium chloride was added to the mixture while maintaining a nitrogen atmosphere, and 10ml of water was further added thereto. The mixture was extracted with chloroform and a saturated saline solution and washed, and then anhydrous sodium sulfate was added thereto and dried overnight. The obtained product was subjected to vacuum concentration in which solvent was completely removed with a vacuum pump. As a result, 0.589g (yield 92.3%) of product consisting of a mixture of cyclic oligo-lactate and chain oligo-lactate was obtained with a weight ratio between cyclic oligomer and chain oligomer being 80 : 20.

[0046] A general view of NMR of the product obtained in Example 3 is shown in Figure 7, and scale views of a part of Figure 7 are shown in Figures 8 and 9.

Example 4

[0047] A THF solution (2ml) in which 0.074g (1.00mmol) of tert-butanol was dissolved was added to a 25ml double-cap eggplant-shaped flask under a nitrogen atmosphere, and cooled to -78°C in a dry ice/acetone bath. Then, 0.64ml (1.00mmol) of n-butyllithium was added thereto and the mixture was stirred for 15 minutes. Further, a THF solution (2ml) in which 0.434g (3.01mmol) of (3R,6R)-(+)-3,6-dimethyl-1,4-dioxane-2,5-dione was dissolved was added thereto and stirred, and the temperature was gradually raised to room temperature over 2.5 hours.

[0048] After completion of stirring, 2ml of saturated ammonium chloride was added to the mixture while maintaining a nitrogen atmosphere, and 10ml of water was further added thereto. The mixture was extracted with chloroform and a saturated saline solution and washed, and then anhydrous sodium sulfate was added thereto and dried overnight. The obtained product was subjected to vacuum concentration in which solvent was completely removed with a vacuum pump. As a result, 0.537g (yield 82.5%) of cyclic oligo-lactate wherein all asymmetric carbon atoms have an R configuration, was obtained.

[0049] An MS spectrum of the product obtained in Example 4 is shown in Figure 10. In addition, a general view of NMR of the product obtained in Example 4 is shown in Figure 11, and scale views of a part of Figure 11 are shown in Figures 12 and 13.

Example 5

[0050] A THF solution (2ml) in which 0.117g (1.06mmol) of thiophenol was dissolved was added to a 50ml double-cap eggplant-shaped flask under a nitrogen atmosphere, and cooled to -78°C in a dry ice/acetone bath. Then, 0.64ml

(1.00mmol) of n-butyllithium was added thereto and the mixture was stirred for 15 minutes. Further, a THF solution (2ml) in which 0.576g (4.00mmol) of (3R,6R)-(+)-3,6-dimethyl-1,4-dioxane-2,5-dione was dissolved was added thereto and stirred, and the temperature was gradually raised to room temperature over 4 hours.

[0051] After completion of stirring, 2ml of saturated ammonium chloride was added to the mixture while maintaining a nitrogen atmosphere, and 10ml of water was further added thereto. The mixture was extracted with chloroform and a saturated saline solution and washed, and then anhydrous sodium sulfate was added thereto and dried overnight. The obtained product was subjected to vacuum concentration in which solvent was completely removed with a vacuum pump. As a result, 0.612g (yield 88.3%) of product was obtained. It was confirmed by NMR analysis that this product comprised cyclic oligo-lactate and chain oligo-lactate at a weight ratio of 96 : 4.

[0052] 0.238g of the product was isolated and purified using silica gel chromatography (solvent; hexane : ether = 1 : 2) to obtain 5 fractions (fraction Nos. 10-1 to 10-5).

[0053] A general view of NMR of the product obtained in Example 5 is shown in Figure 14, and scale views of a part of Figure 14 are shown in Figures 15 and 16.

Example 6

[0054] 3ml of THF solution containing 0.089g (1mmol) of S-lactic acid amide was added to a 50ml double-cap eggplant-shaped flask at room temperature under a nitrogen atmosphere, and 0.64ml (1.00mmol) of n-butyllithium was reacted therewith at -78°C followed by stirring for 15 minutes. Further, 2ml of THF solution containing 0.576g (4mmol) of L-(-)-lactide was added thereto and reacted therewith for 30 minutes, and then the temperature was raised from -78°C to 0°C followed by reaction for 1.5 hours. Subsequently, the temperature was further raised to room temperature by addition of 5ml of saturated ammonium chloride solution. After the mixture was extracted with chloroform, the organic layer was washed with a saturated saline solution, and dried with anhydrous sodium sulfate followed by vacuum concentration (NMR sa0140), to obtain a residue.

[0055] A general view of NMR of the product obtained in Example 6 is shown in Figure 17, and scale views of a part of Figure 17 are shown in Figures 18 and 19.

Example 7

[0056] A THF solution (2ml) in which 0.090g (1.00mmol) of trimethylsilanol was dissolved was added to a 25ml double-cap eggplant-shaped flask under a nitrogen atmosphere, and cooled to 0°C. Then, 0.64ml (1.00mmol) of n-butyllithium was added thereto and the mixture was stirred for 15 minutes. Further, a THF solution (2ml) in which 0.434g (3.01mmol) of (3R,6R)-(+)-3,6-dimethyl-1,4-dioxane -2,5-dione was dissolved was added thereto and stirred, and the temperature was gradually raised to room temperature over 2.5 hours.

[0057] After completion of stirring, 2ml of saturated ammonium chloride was added to the mixture while maintaining a nitrogen atmosphere, and 10ml of water was further added thereto. The mixture was extracted with chloroform and a saturated saline solution and washed, and then anhydrous sodium sulfate was added thereto and dried overnight. The obtained product was subjected to vacuum concentration in which solvent was completely removed with a vacuum pump. As a result, 0.537g (yield 82.5%) of cyclic oligo-lactate wherein all asymmetric carbon atoms have an R configuration, was obtained.

[0058] A general view of NMR of the product obtained in Example 7 is shown in Figure 20, and scale views of a part of Figure 20 are shown in Figures 21 and 22.

Example 8

[0059] A THF solution (2ml) in which 0.276g (1.00mmol) of triphenylsilanol was dissolved was added to a 25ml double-cap eggplant-shaped flask under a nitrogen atmosphere, and cooled to 0°C. Then, 0.64ml (1.00mmol) of n-butyllithium was added thereto and the mixture was stirred for 15 minutes. Further, a THF solution (2ml) in which 0.434g (3.01mmol) of (3R,6R)-(+)-3,6-dimethyl-1,4-dioxane -2,5-dione was dissolved was added thereto and stirred, and the temperature was gradually raised to room temperature over 2.5 hours.

[0060] After completion of stirring, 2ml of saturated ammonium chloride was added to the mixture while maintaining a nitrogen atmosphere, and 10ml of water was further added thereto. The mixture was extracted with chloroform and a saturated saline solution and washed, and then anhydrous sodium sulfate was added thereto and dried overnight. The obtained product was subjected to vacuum concentration in which solvent was completely removed with a vacuum pump. As a result, 0.537g (yield 82.5%) of cyclic oligo-lactate wherein all asymmetric carbon atoms have an R configuration, was obtained.

[0061] A general view of NMR of the product obtained in Example 8 is shown in Figure 23, and scale views of a part of Figure 23 are shown in Figures 24 and 25.

Example 9

[0062] A THF solution (2ml) in which 0.132g (1.00mmol) of t-butyldimethylsilanol was dissolved was added to a 25ml double-cap eggplant-shaped flask under a nitrogen atmosphere, and cooled to 0°C. Then, 0.64ml (1.00mmol) of n-butyllithium was added thereto and the mixture was stirred for 15 minutes. Further, a THF solution (2ml) in which 0.434g (3.01mmol) of (3R,6R)-(+)-3,6-dimethyl-1,4-dioxane -2,5-dione was dissolved was added thereto and stirred, and the temperature was gradually raised to room temperature over 2.5 hours.

[0063] After completion of stirring, 2ml of saturated ammonium chloride was added to the mixture while maintaining a nitrogen atmosphere, and 10ml of water was further added thereto. The mixture was extracted with chloroform and a saturated saline solution and washed, and then anhydrous sodium sulfate was added thereto and dried overnight. The obtained product was subjected to vacuum concentration in which solvent was completely removed with a vacuum pump. As a result, 0.537g (yield 82.5%) of cyclic oligo-lactate wherein all asymmetric carbon atoms have an R configuration, was obtained.

[0064] A general view of NMR of the product obtained by Example 9 is shown in Figure 26, and a scale view of a part of Figure 26 is shown in Figure 27.

Example 10

[0065] 3ml of THF solution containing 0.118g (1mmol) of ethyl S-lactate was added to a 50ml double-cap eggplant-shaped flask at room temperature under a nitrogen atmosphere, and 0.64ml (1.00mmol) of n-butyllithium was reacted therewith at -78°C followed by stirring for 15 minutes. Further, 2ml of THF solution containing 0.576g (4mmol) of L-(-)-lactide was added thereto and reacted therewith for 30 minutes, and then the temperature was raised from -78°C to 0°C followed by reaction for 1.5 hours. Subsequently, the temperature was further raised to room temperature by addition of 5ml of saturated ammonium chloride solution. After the mixture was extracted with chloroform, the organic layer was washed with a saturated saline solution, and dried with anhydrous sodium sulfate followed by vacuum concentration (NMR sa0140), to obtain the residue.

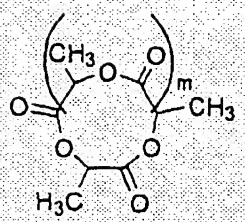
[0066] An MS spectrum of the product obtained in Example 10 is shown in Figure 28. In addition, a general view of NMR of the product obtained in Example 10 is shown in Figure 29, and scale views of a part of Figure 29 are shown in Figures 30 and 31.

INDUSTRIAL APPLICABILITY

[0067] According to the method for producing a cyclic lactic acid oligomer of the present invention, a cyclic lactic acid oligomer can be produced at good yield, and its industrial significance is great. In addition, a cyclic lactic acid oligomer produced by the production method of the present invention is useful as a tumor cell growth inhibiting agent, antineoplastic agent, preventive agent against cancer metastasis, QOL improving agent for cancer patients, immune activating agent, therapeutic agent for diabetes, antiobestic agent, an agent for promoting glycogen accumulation or an agent for enhancing physical fitness. Furthermore, the cyclic lactic acid oligomer is useful not only as a medicament, but also as various types of health foods and diet supplements including soft drinks, drinkable preparations, health foods, specific hygienic foods, functional foods, function activating food, nutritional supplementary foods, supplements, feed, feed additives, and the like.

Claims

1. A method for producing a cyclic lactic acid oligomer represented by the following formula (1):



(1)

wherein m represents an integer of 1 to 30,
wherein lactides are polymerized in the presence of an alkali metal compound represented by the following formula (2):

$$R\text{-}Y\text{-}Me \qquad (2)$$

wherein

R represents an aliphatic group, aromatic group, $-Si(R^{10})(R^{11})(R^{12})$, $-CH(R^{20})CONR^{21}R^{22}$ or $-CH(R^{30})COOR^{31}$, wherein each of R^{10}, R^{11} and R^{12} independently represents an aliphatic or aromatic group, R^{20} represents an aliphatic group, each of R^{21} and R^{22} independently represents a hydrogen atom, aliphatic group or aromatic group, R^{30} represents an aliphatic group, and R^{31} represents a hydrogen atom, aliphatic group or aromatic group;
Y represents -O-, -S- or $-NR^{40}-$, wherein R^{40} represents a hydrogen atom, aliphatic group or aromatic group; and
Me represents an alkali metal.

2. The method for producing a cyclic lactic acid oligomer according to claim 1, wherein said alkali metal compound is a compound of formula (2) wherein R represents an alkyl group having 1 to 12 carbon atoms, aryl group having 6 to 30 carbon atoms, $-Si(R^{10})(R^{11})(R^{12})$, $-CH(R^{20})CONR^{21}R^{22}$ or $-CH(R^{30})COOR^{31}$, wherein each of R^{10}, R^{11} and R^{12} independently represents an aliphatic or aromatic group, R^{20} represents an aliphatic group, each of R^{21} and R^{22} independently represents a hydrogen atom, aliphatic group or aromatic group, R^{30} represents an aliphatic group, and R^{31} represents a hydrogen atom, aliphatic group or aromatic group.

3. The method for producing a cyclic lactic acid oligomer according to claim 1 or 2, wherein said alkali metal compound is a compound of formula (2) wherein Y is -O- or -S-.

4. The method for producing a cyclic lactic acid oligomer according to any one of claims 1 to 3, wherein said alkali metal compound is a compound of formula (2) wherein Me is lithium.

5. The method for producing a cyclic lactic acid oligomer according to any one of claims 1 to 4, wherein, in formula (1), m is an integer of 1 to 21.

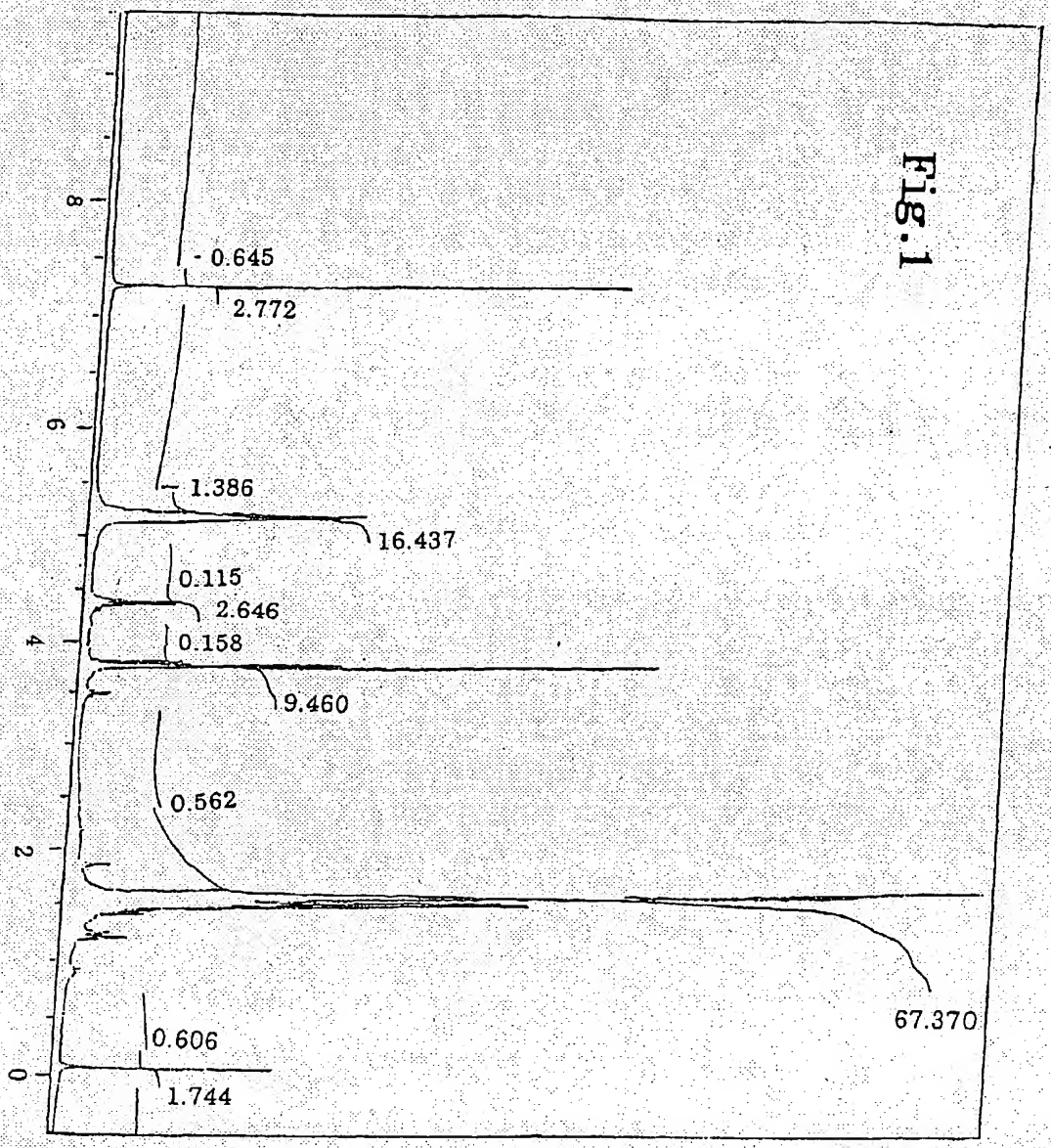
6. The method for producing a cyclic lactic acid oligomer according to any one of claims 1 to 5, wherein said alkali metal compound is any of:

a compound of formula (2) wherein R is an aliphatic group having 4 or more carbon atoms; a compound of formula (2) wherein R is an aromatic group and Y is -S-; or a compound of formula (2) wherein R is $-CH(R^{20})CONR^{21}R^{22}$ wherein R^{20} represents an aliphatic group and each of R^{21} and R^{22} independently represents a hydrogen atom, aliphatic group or aromatic group.

7. The method for producing a cyclic lactic acid oligomer according to claim 6, wherein cyclic lactic acid oligomer is selectively produced substantially free of chain lactic acid oligomer.

8. A cyclic lactic acid oligomer, which is produced by the method for producing a cyclic lactic acid oligomer according to any one of claims 1 to 7.

9. The cyclic lactic acid oligomer according to claim 8, which is substantially free of chain lactic acid oligomer.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1.744

Fig.1

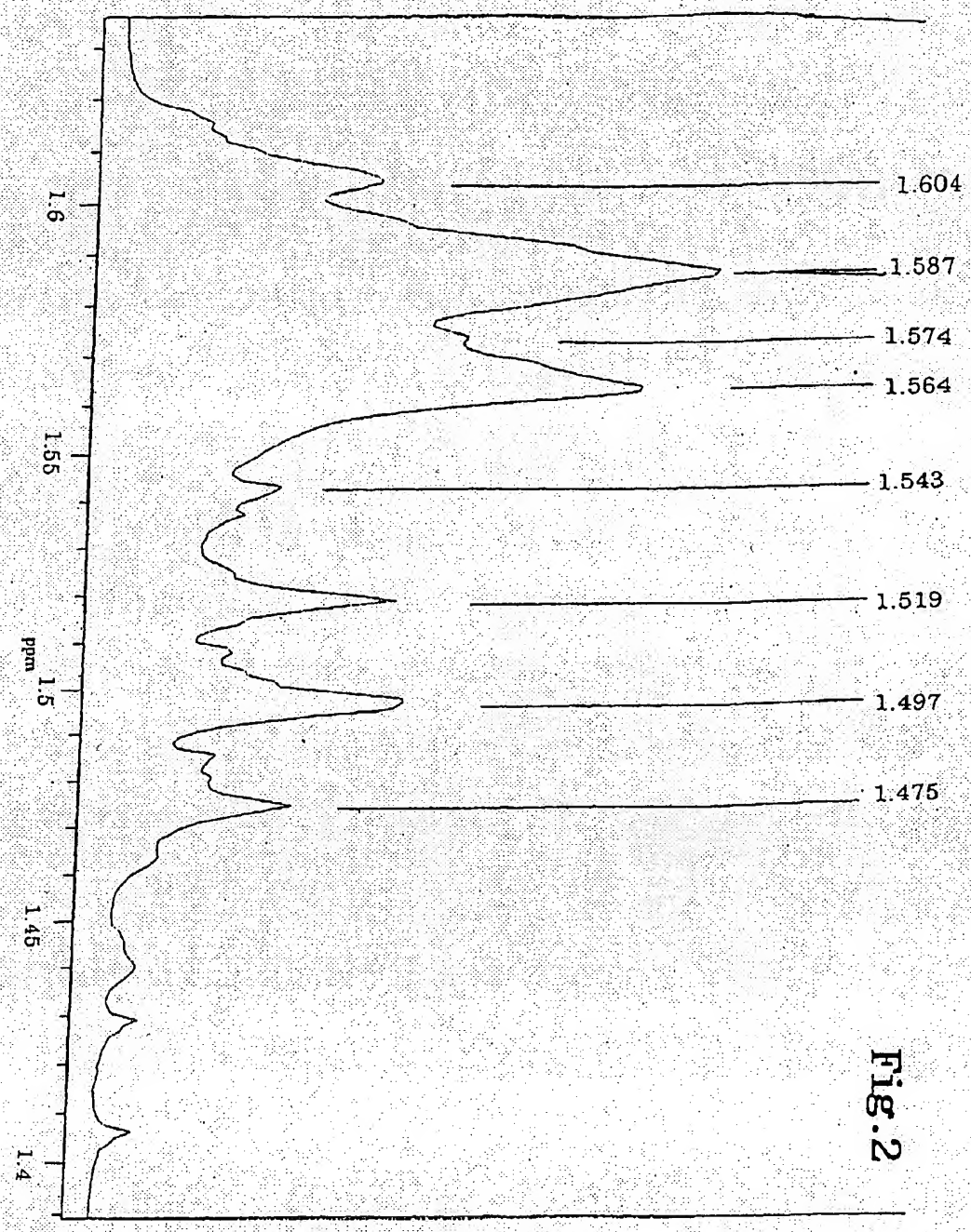

Fig.2

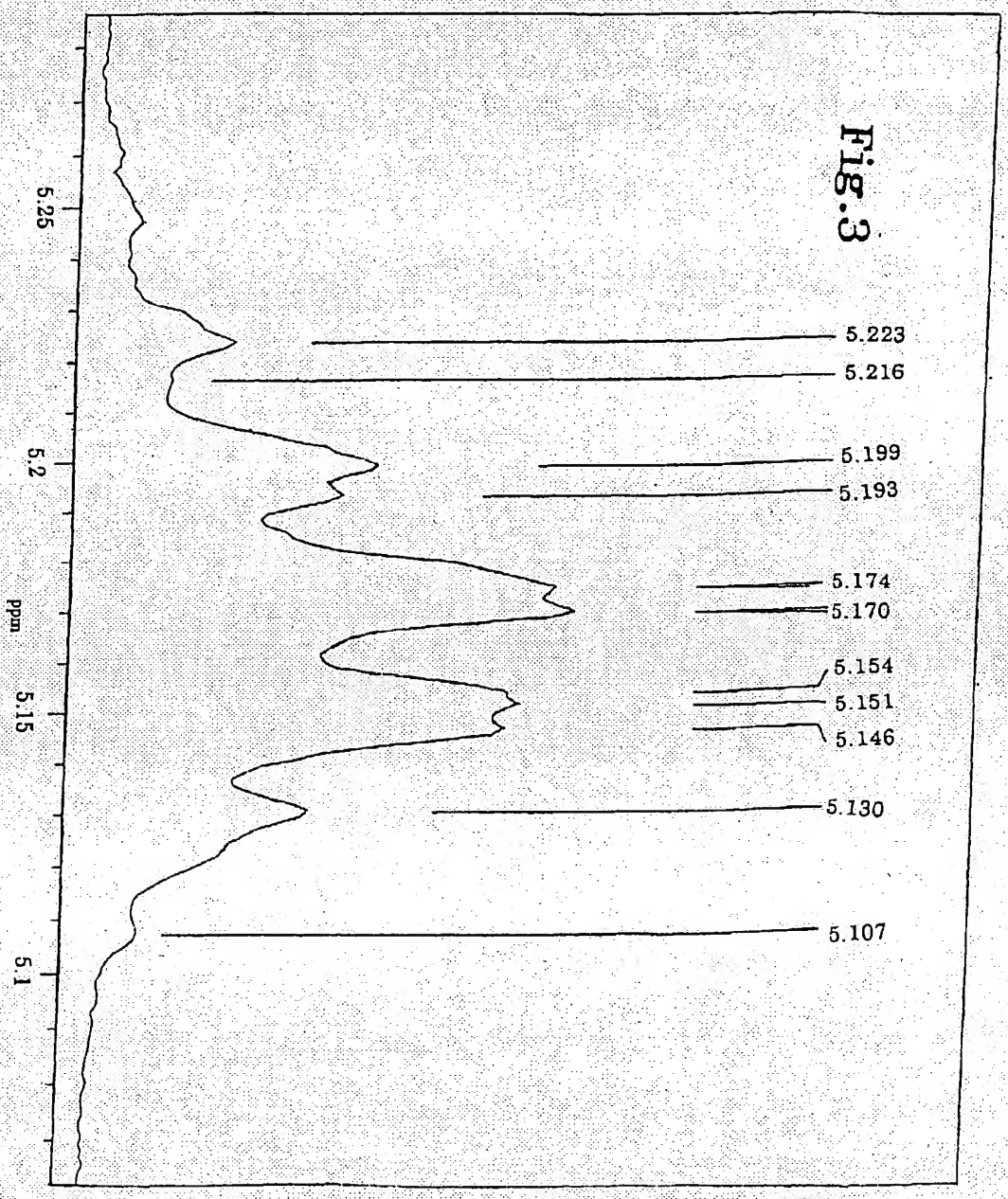
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Fig.3

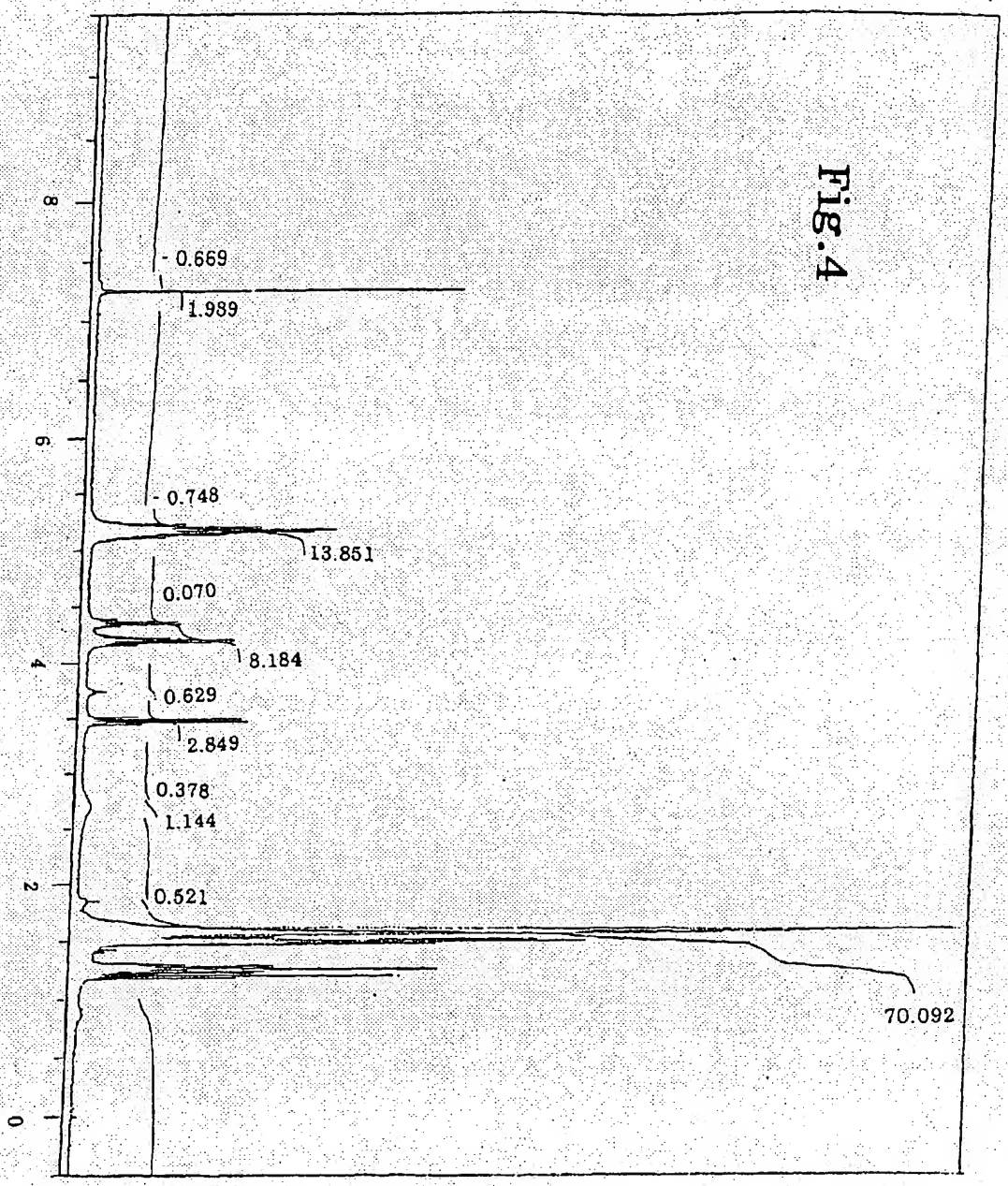
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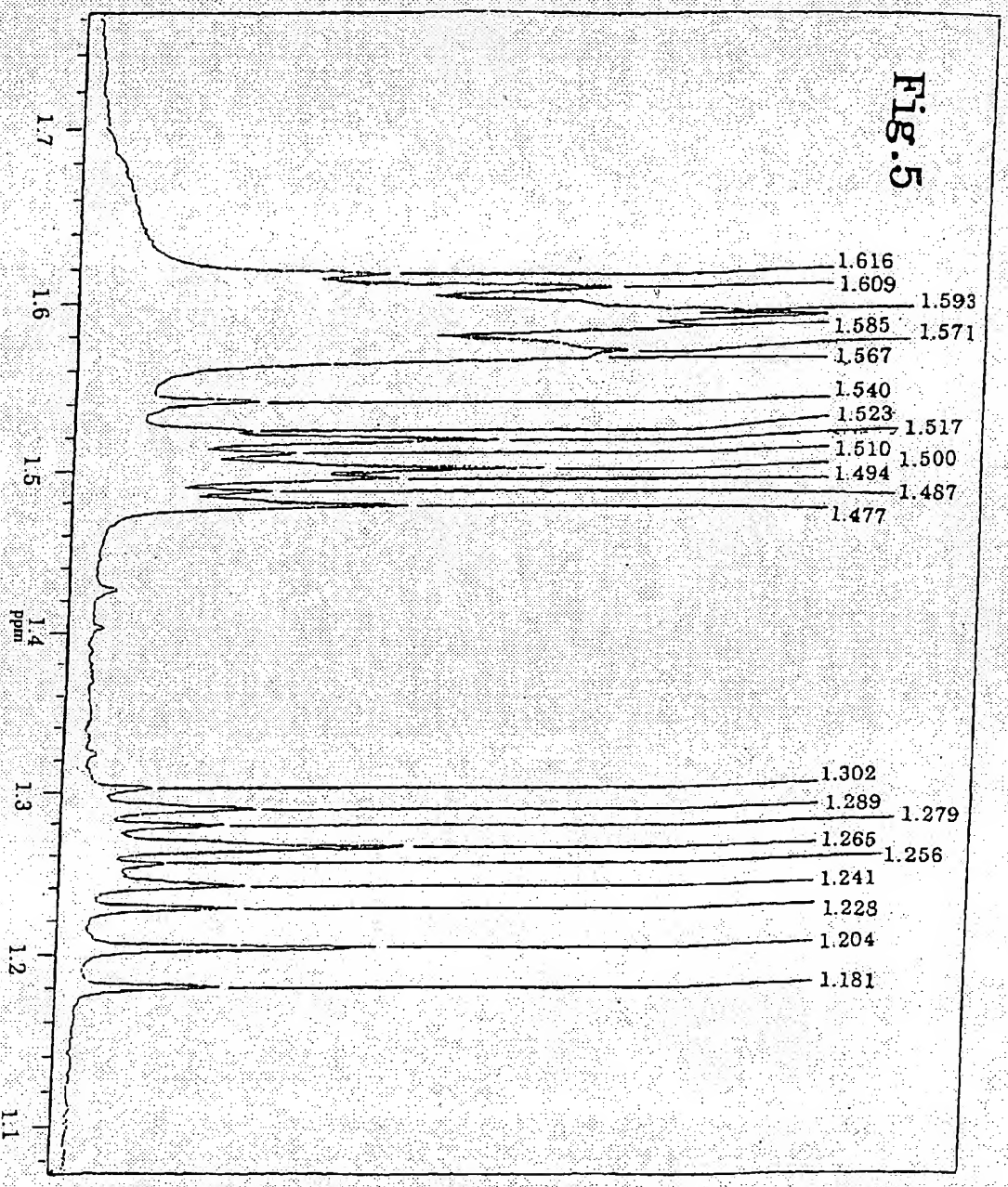
Fig.4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1.181

Fig.5

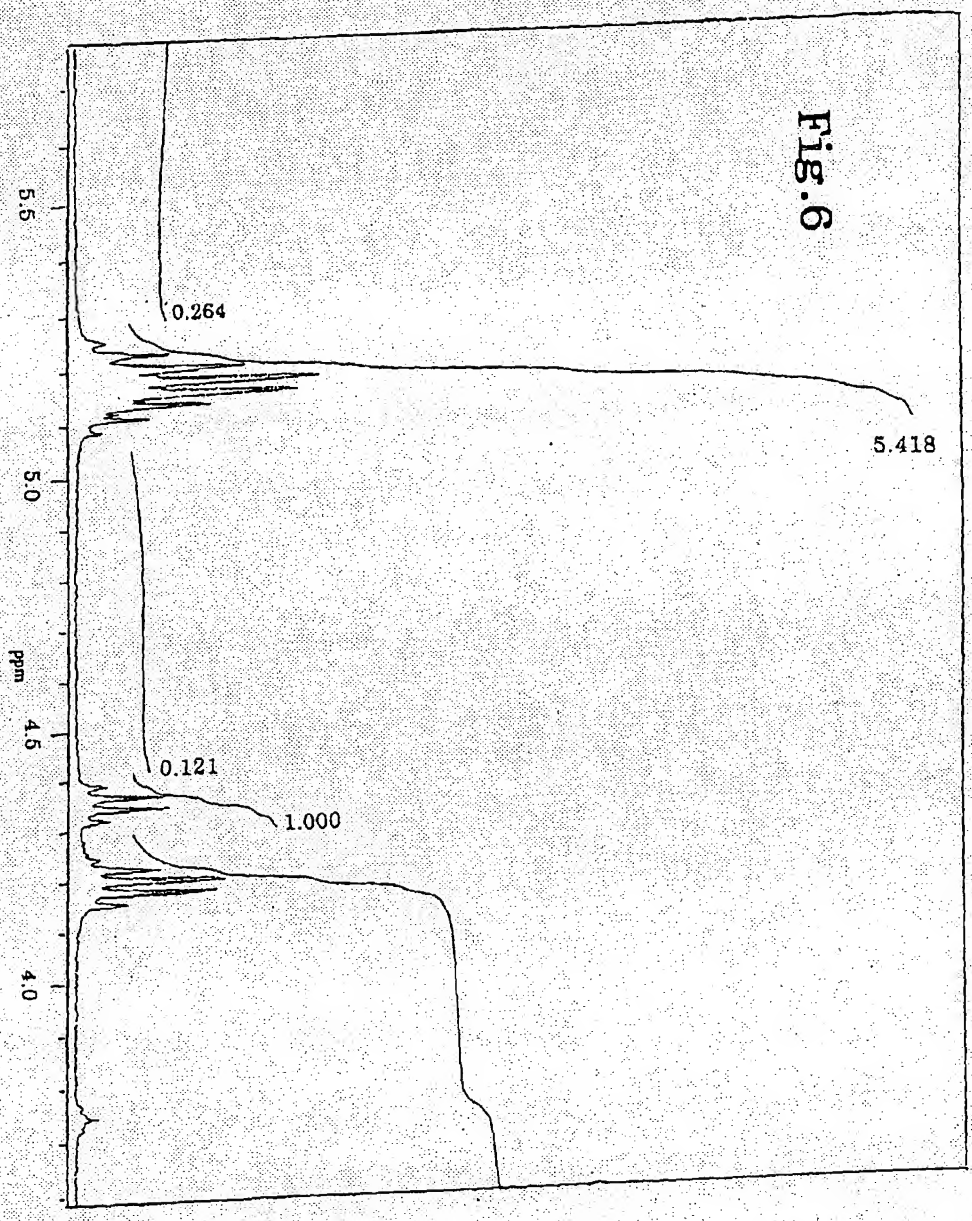


Fig.6

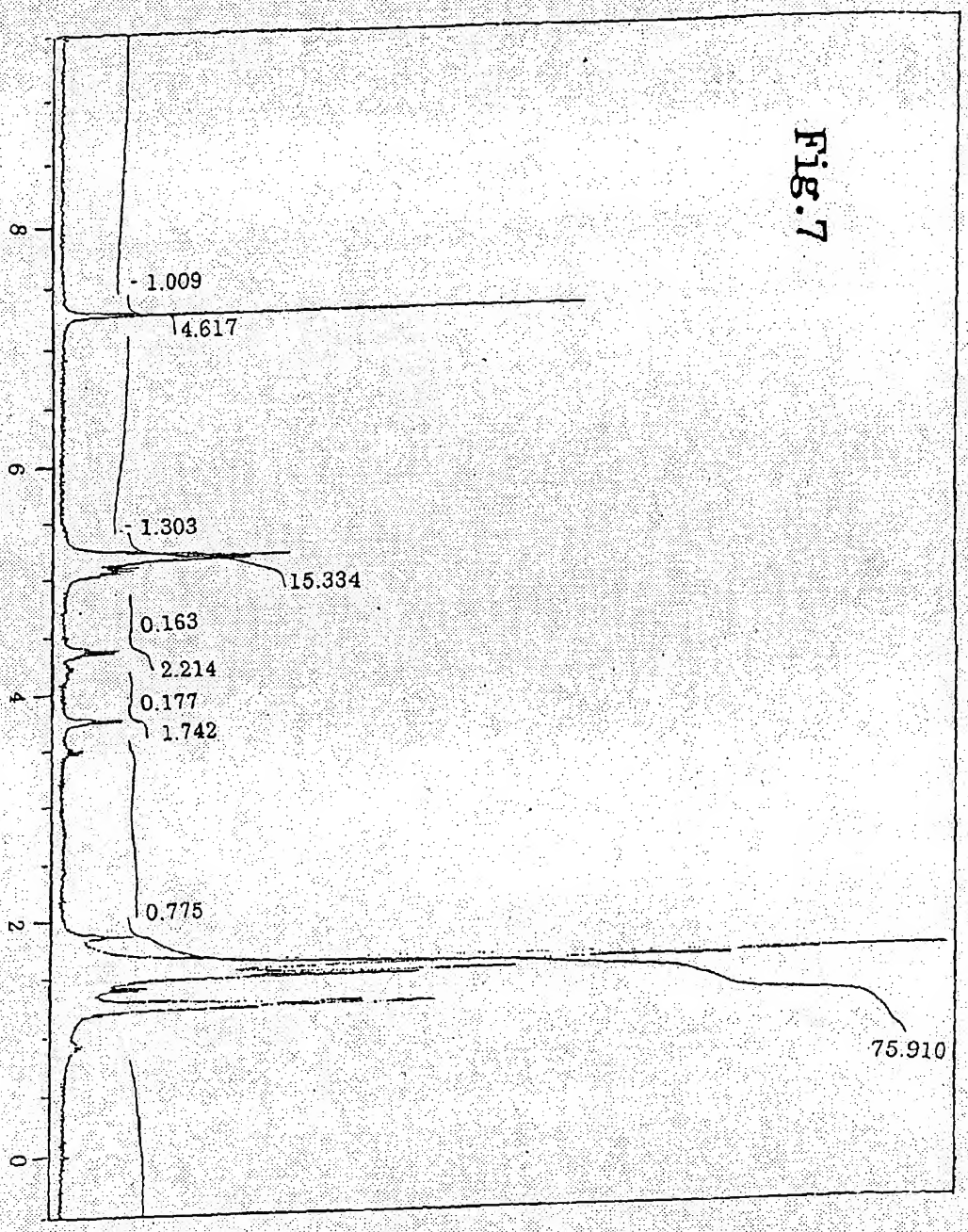
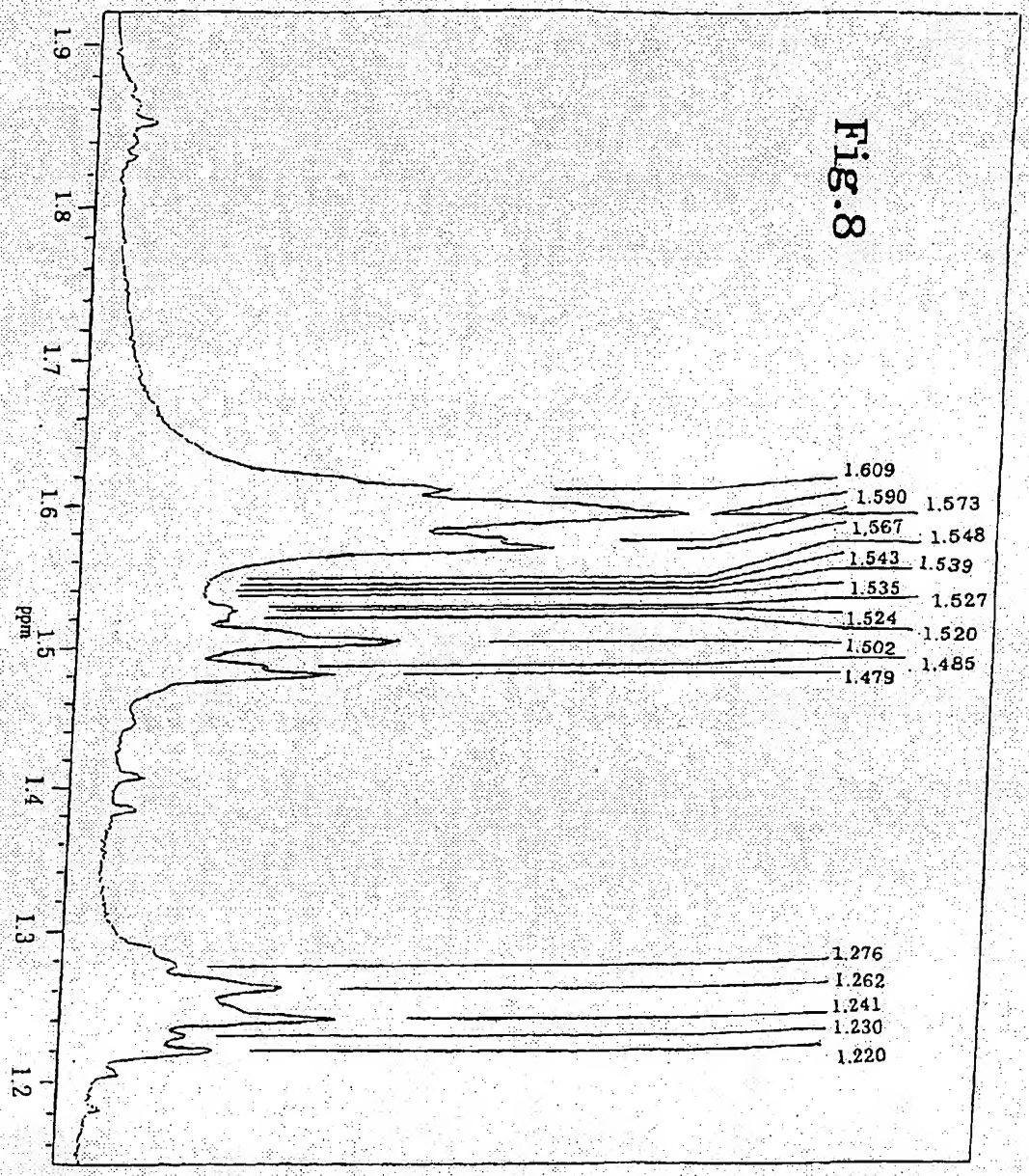


Fig.7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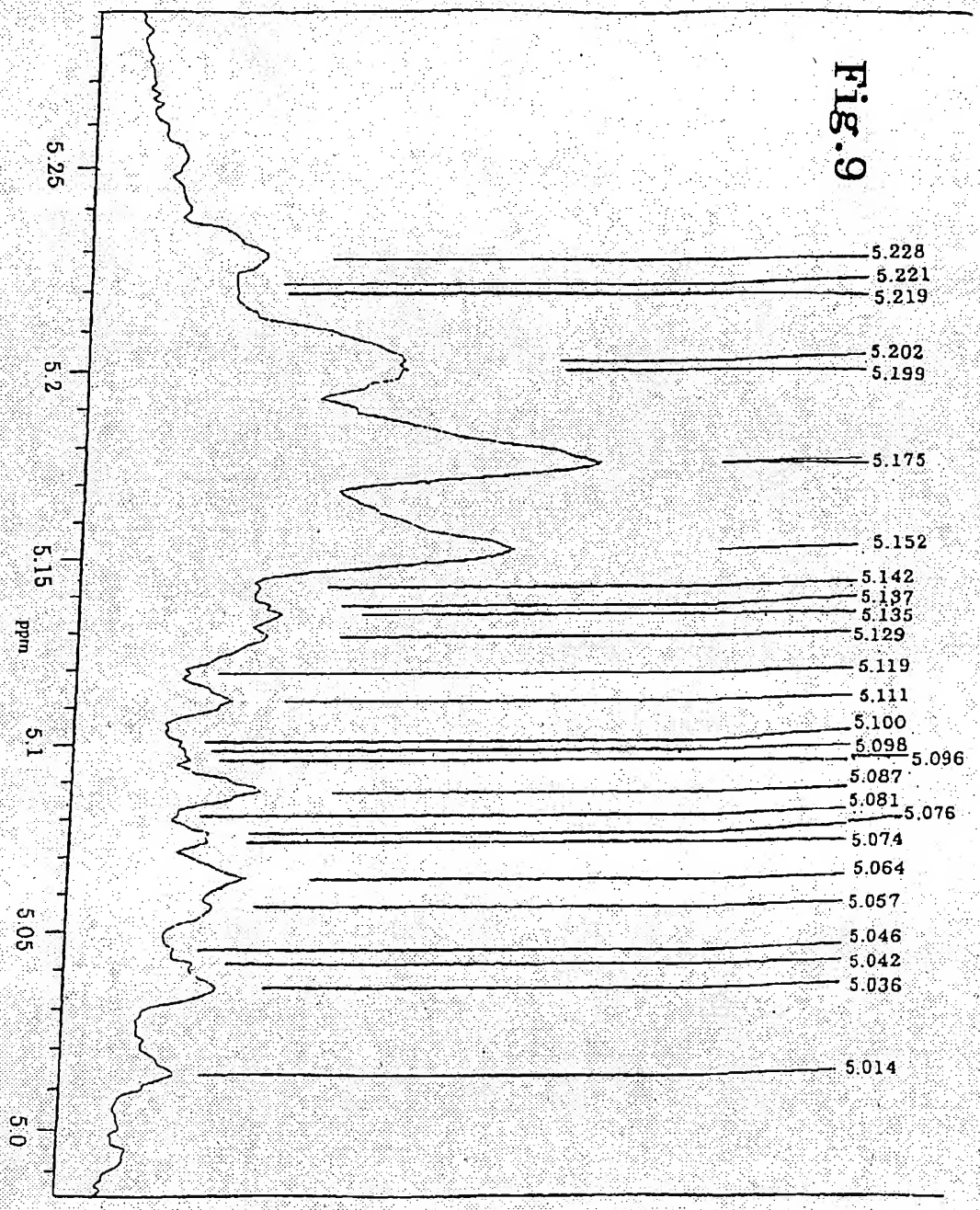
1.220

Fig.8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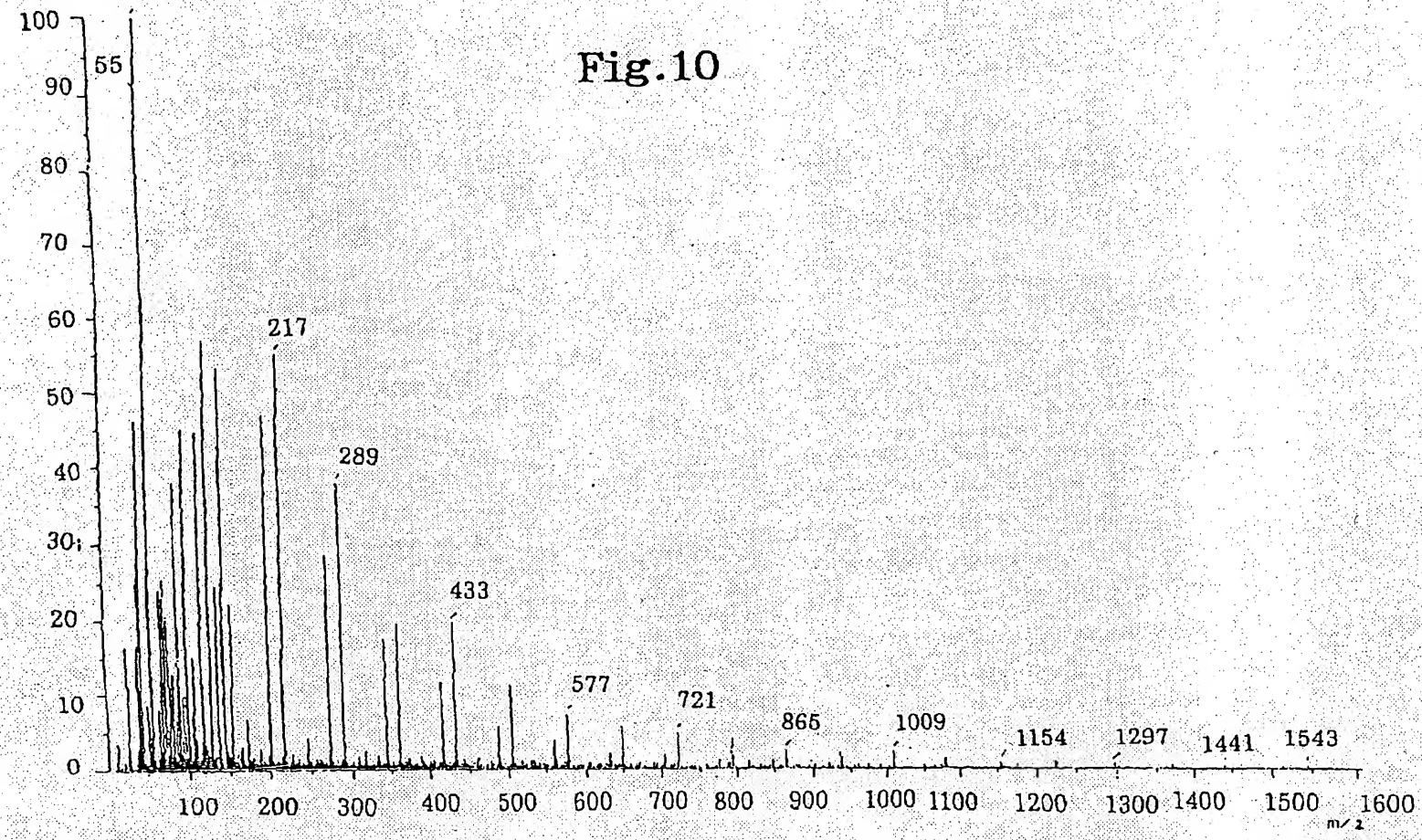
5.036
5.014

Fig.9

Fig.10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1500
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m/z

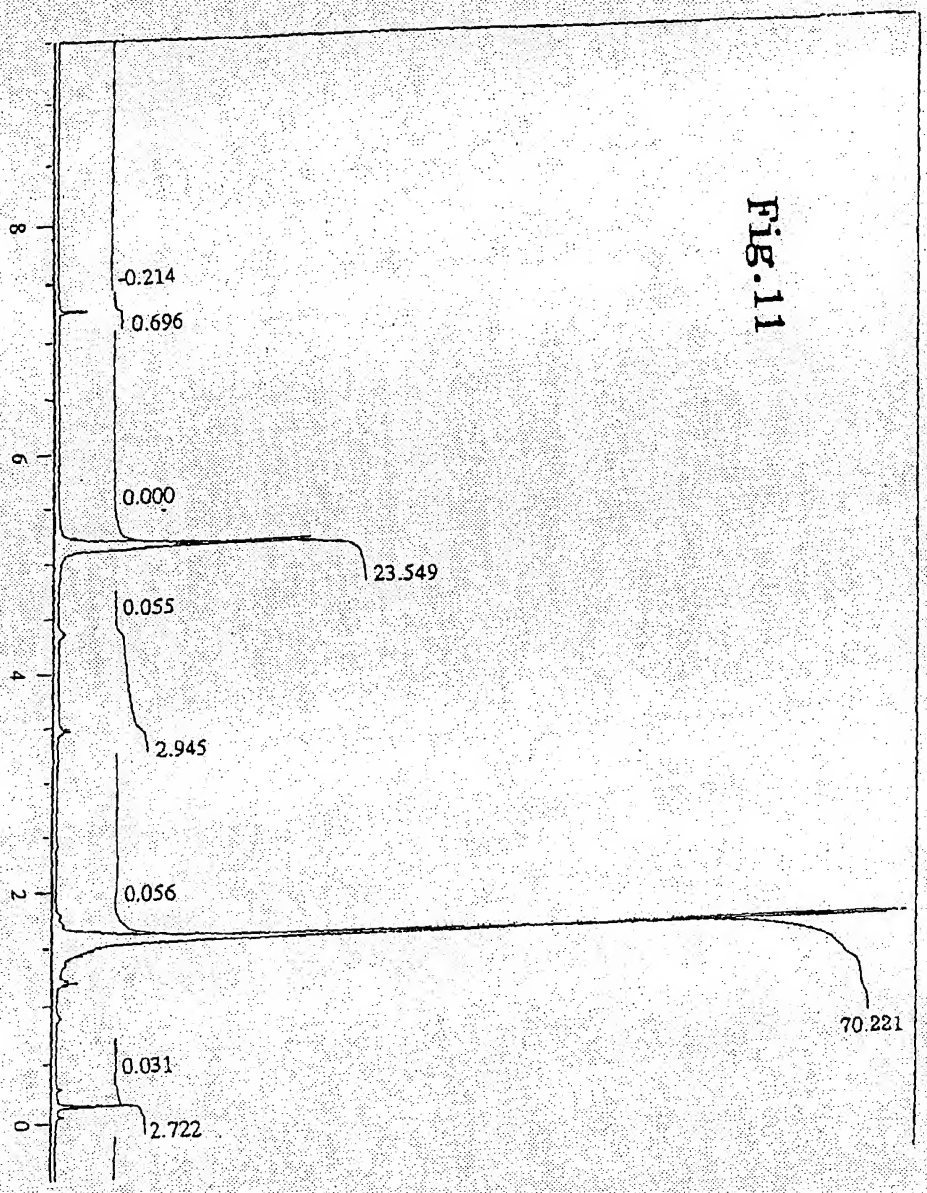


Fig.11

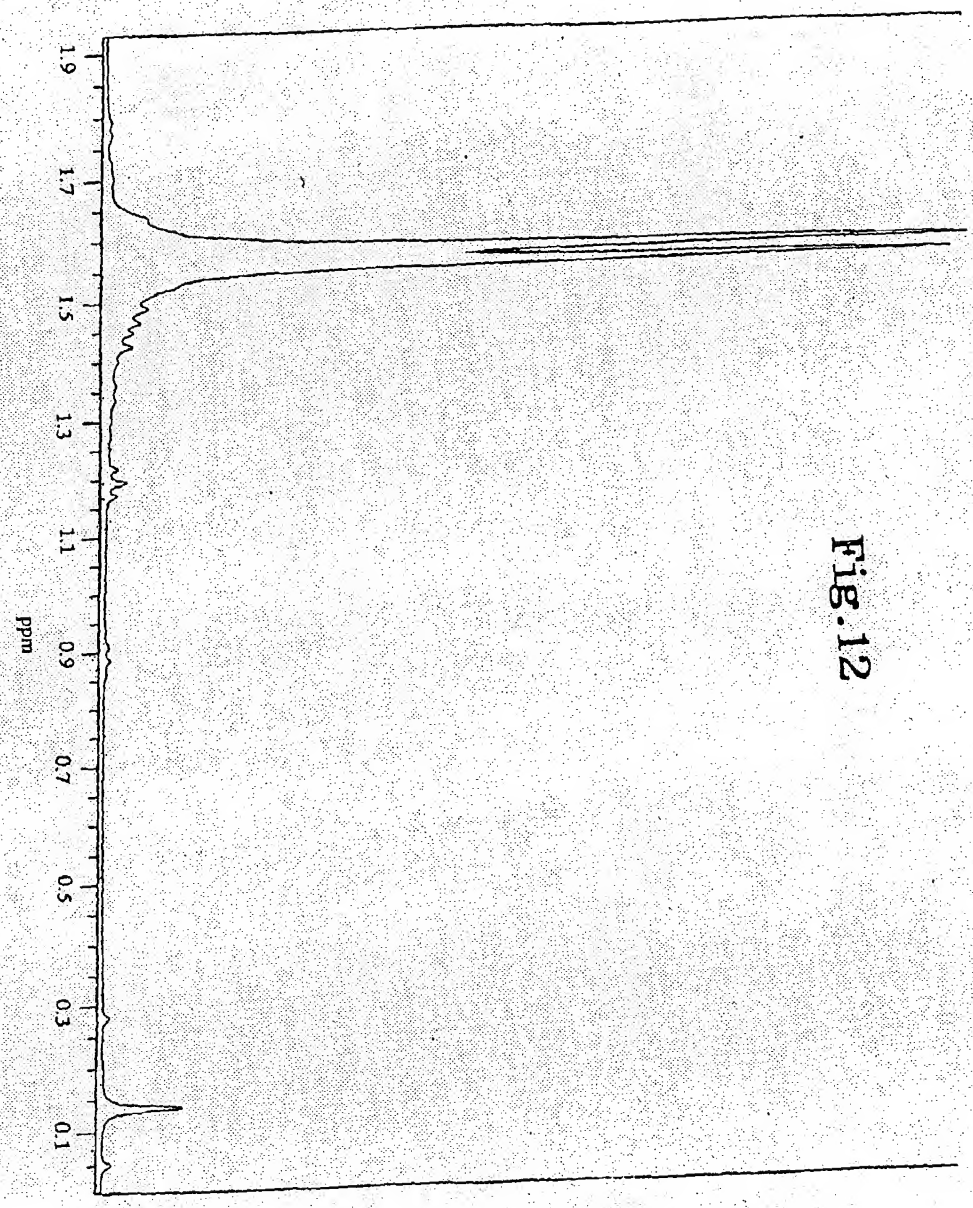


Fig.12

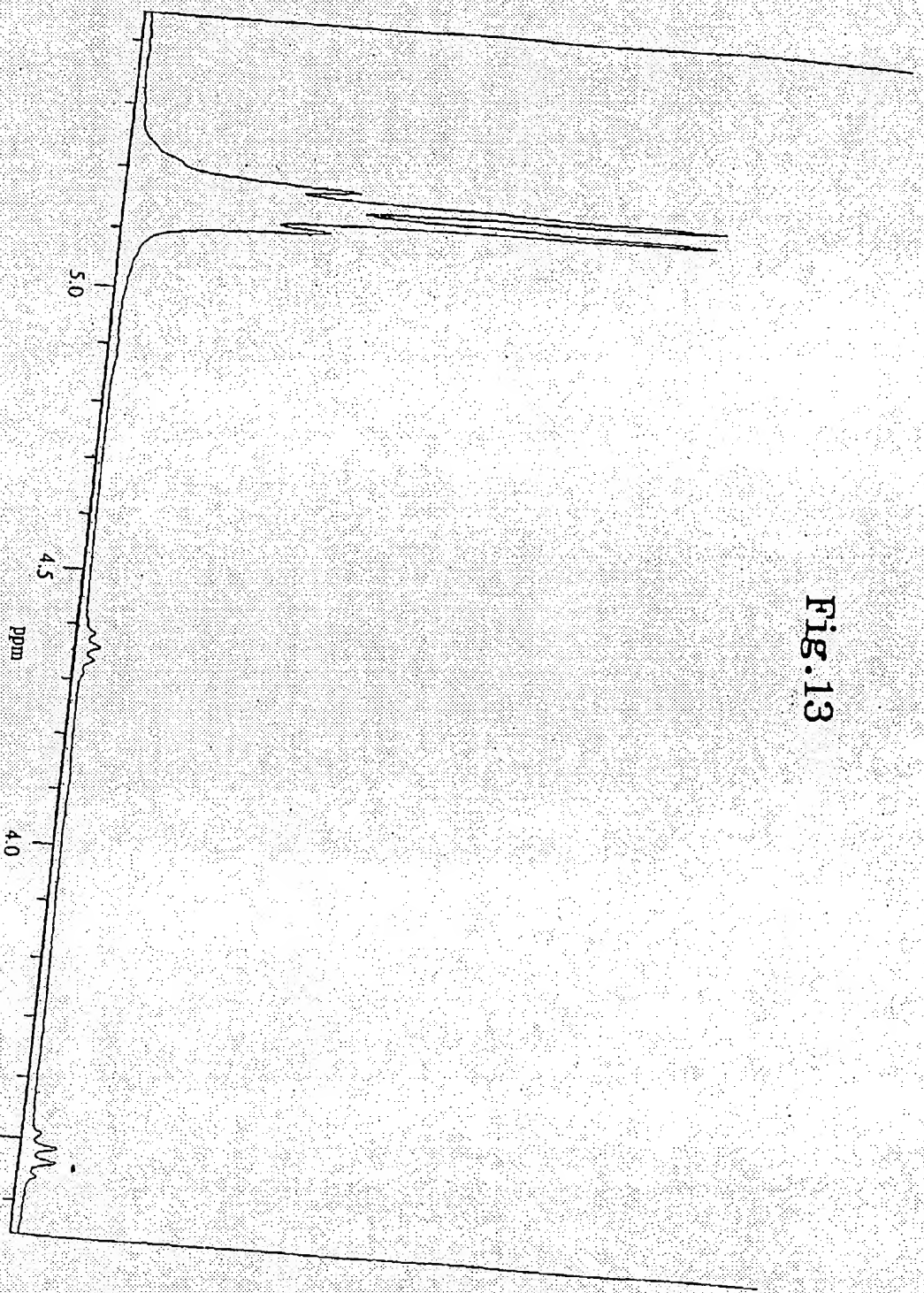
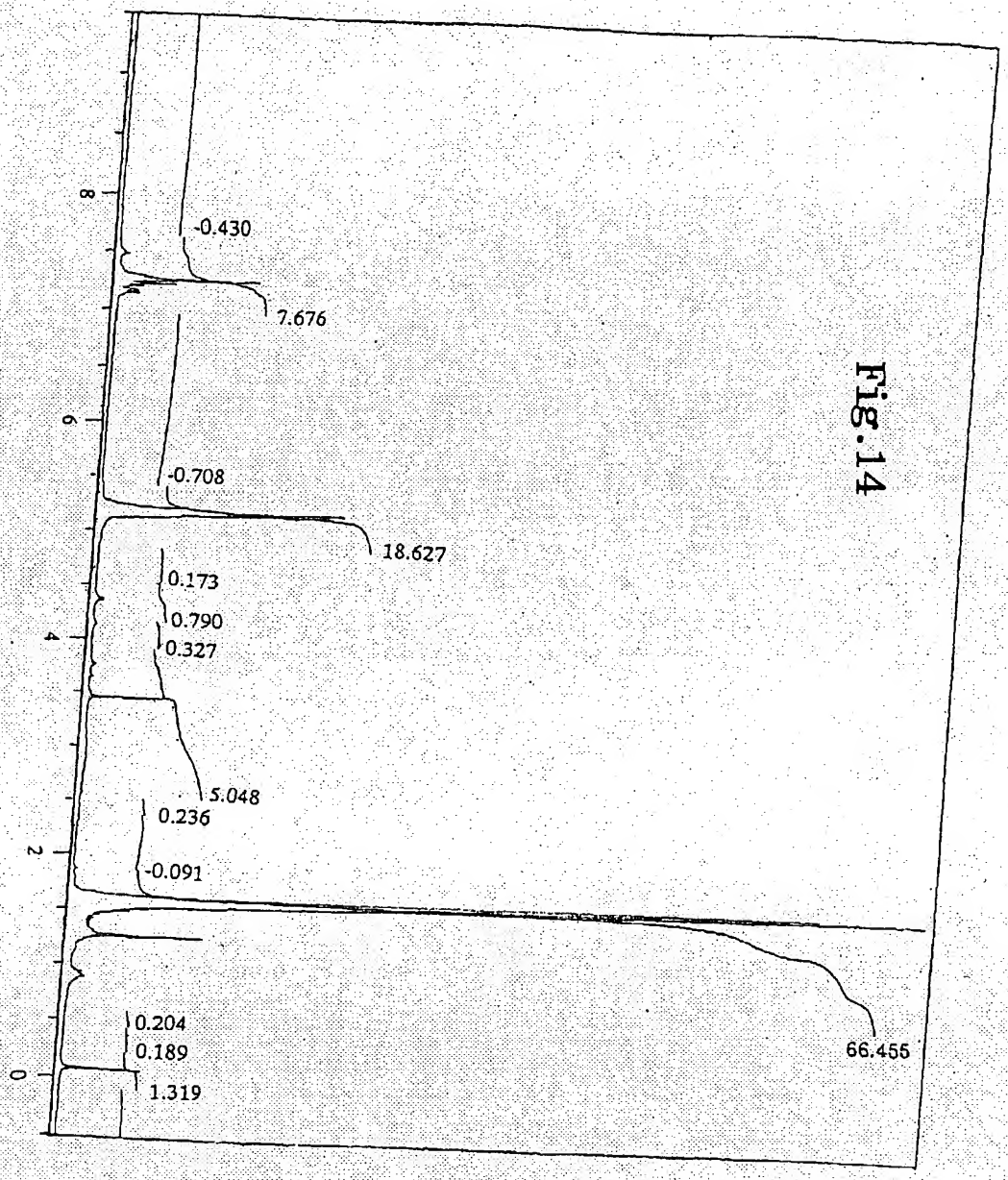


Fig.13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66.455

Fig.14

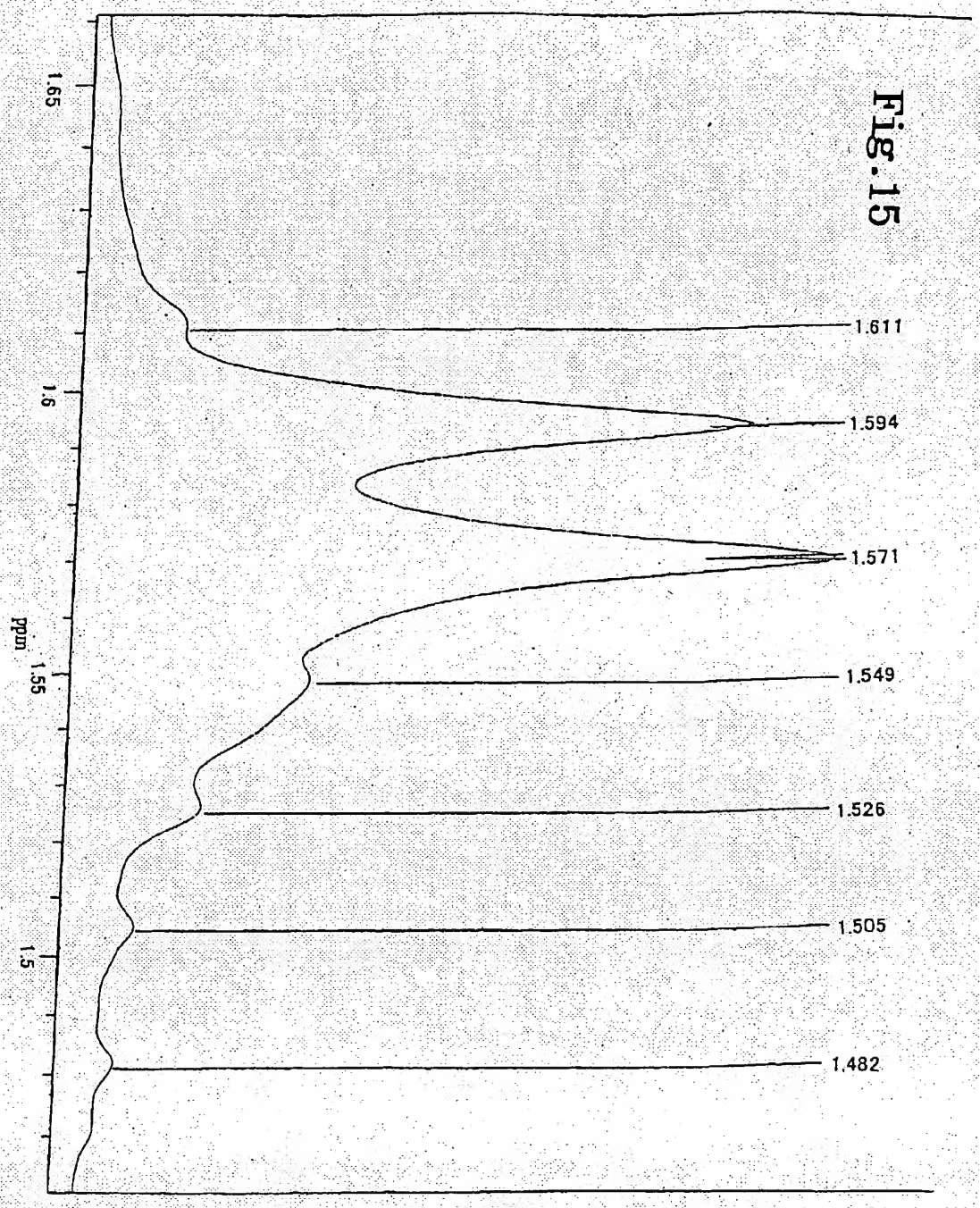

Fig.15

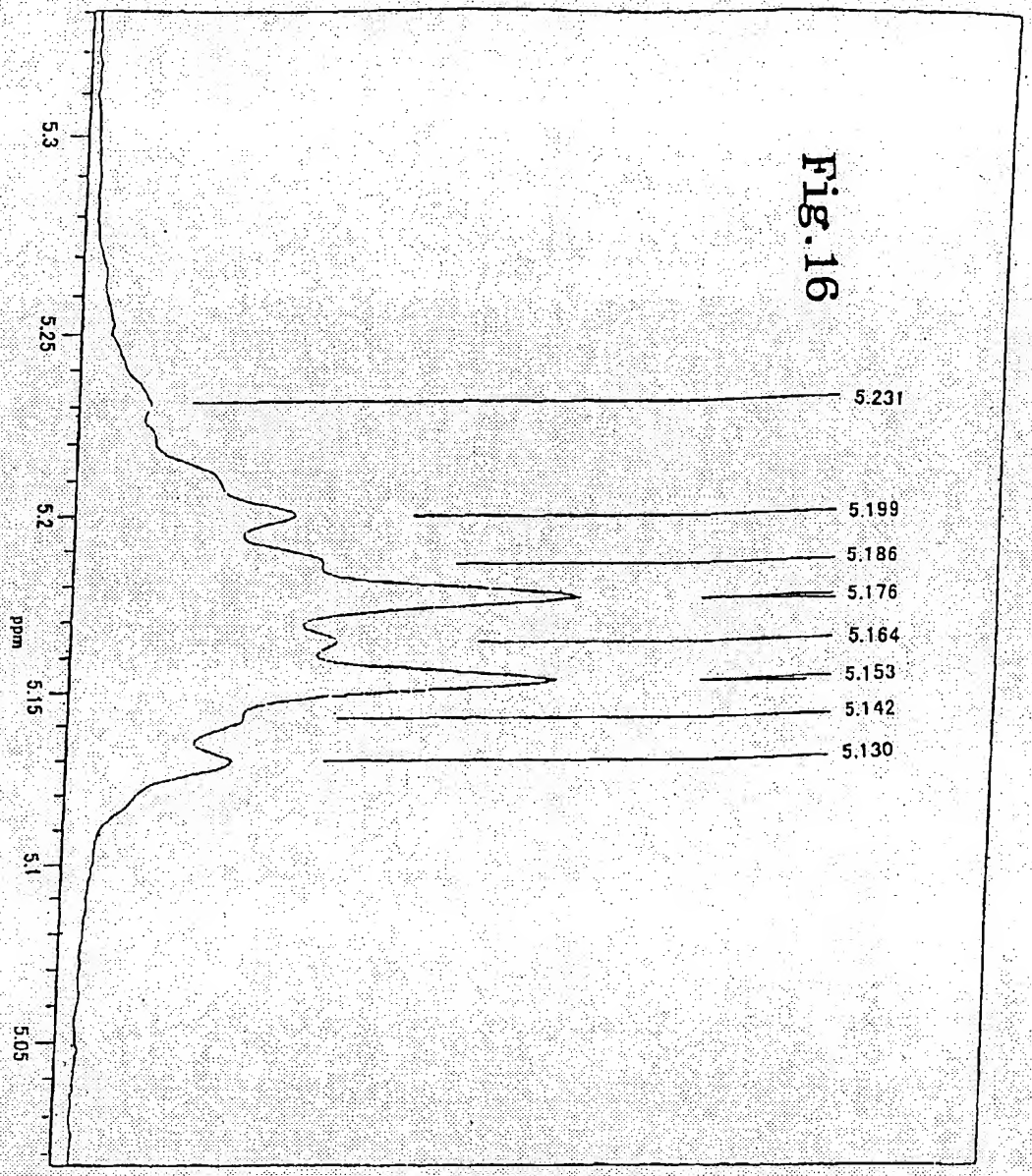
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Fig.16

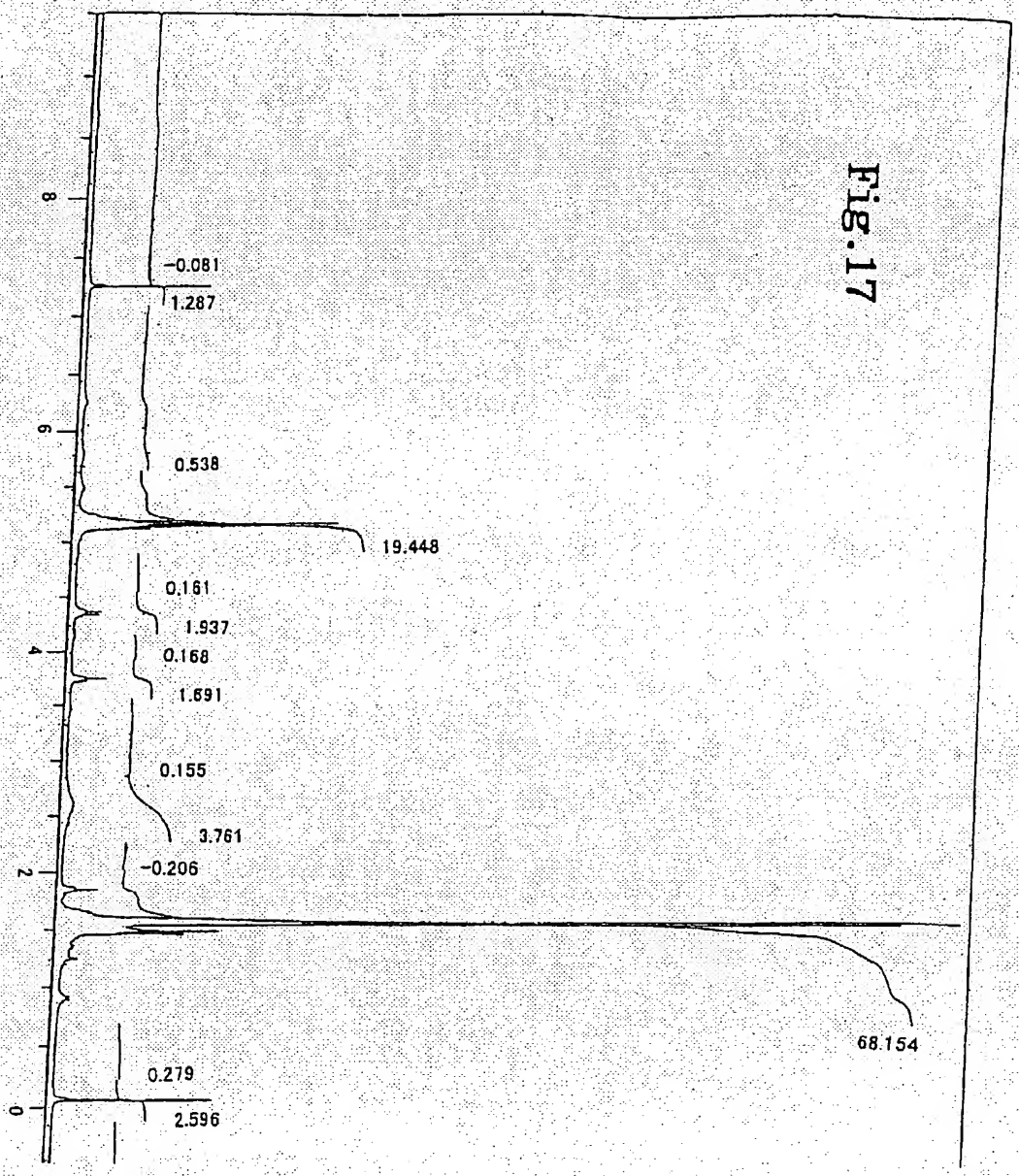
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Fig. 17

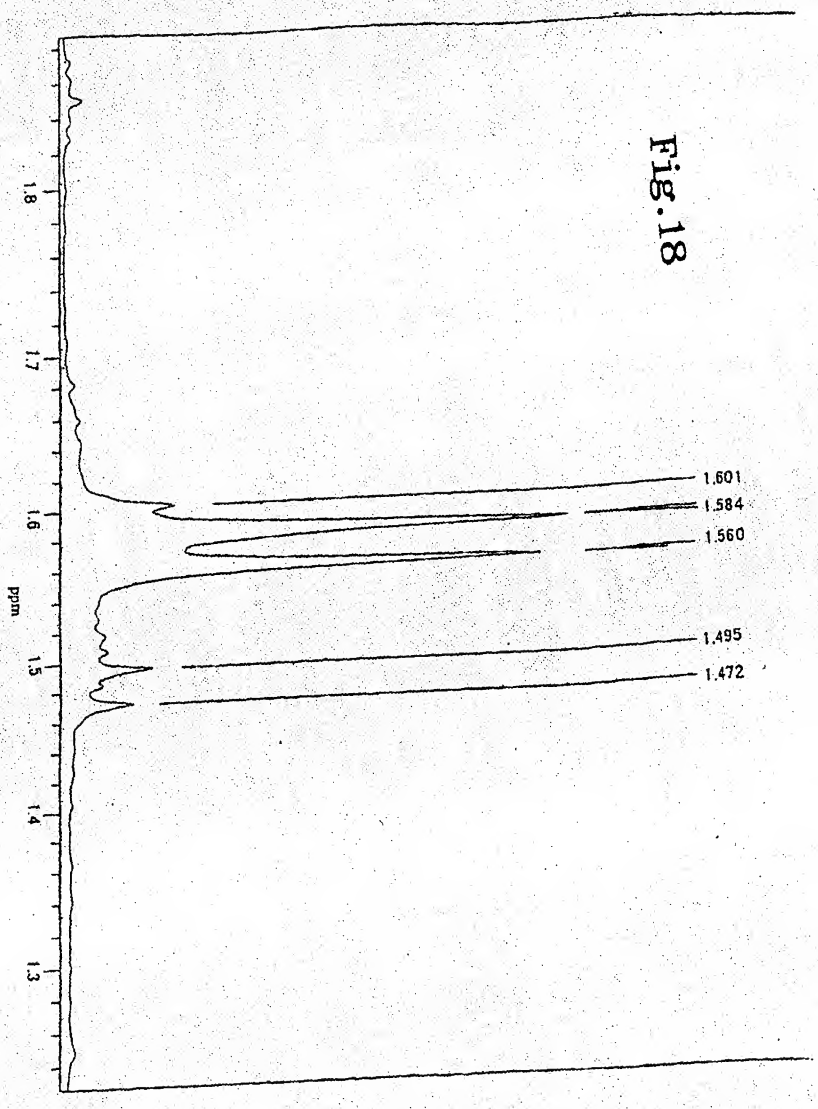


Fig.18

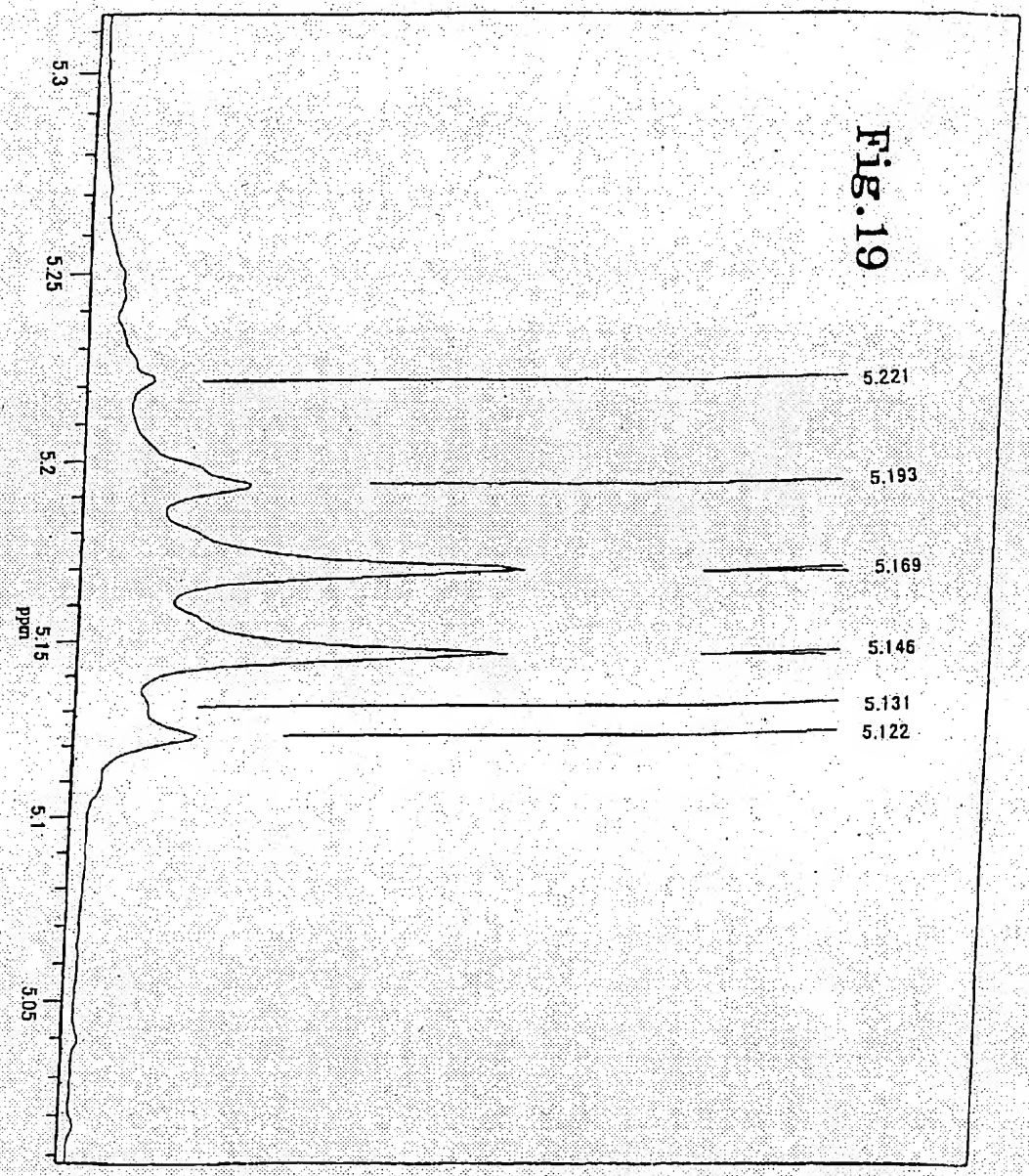


Fig.19

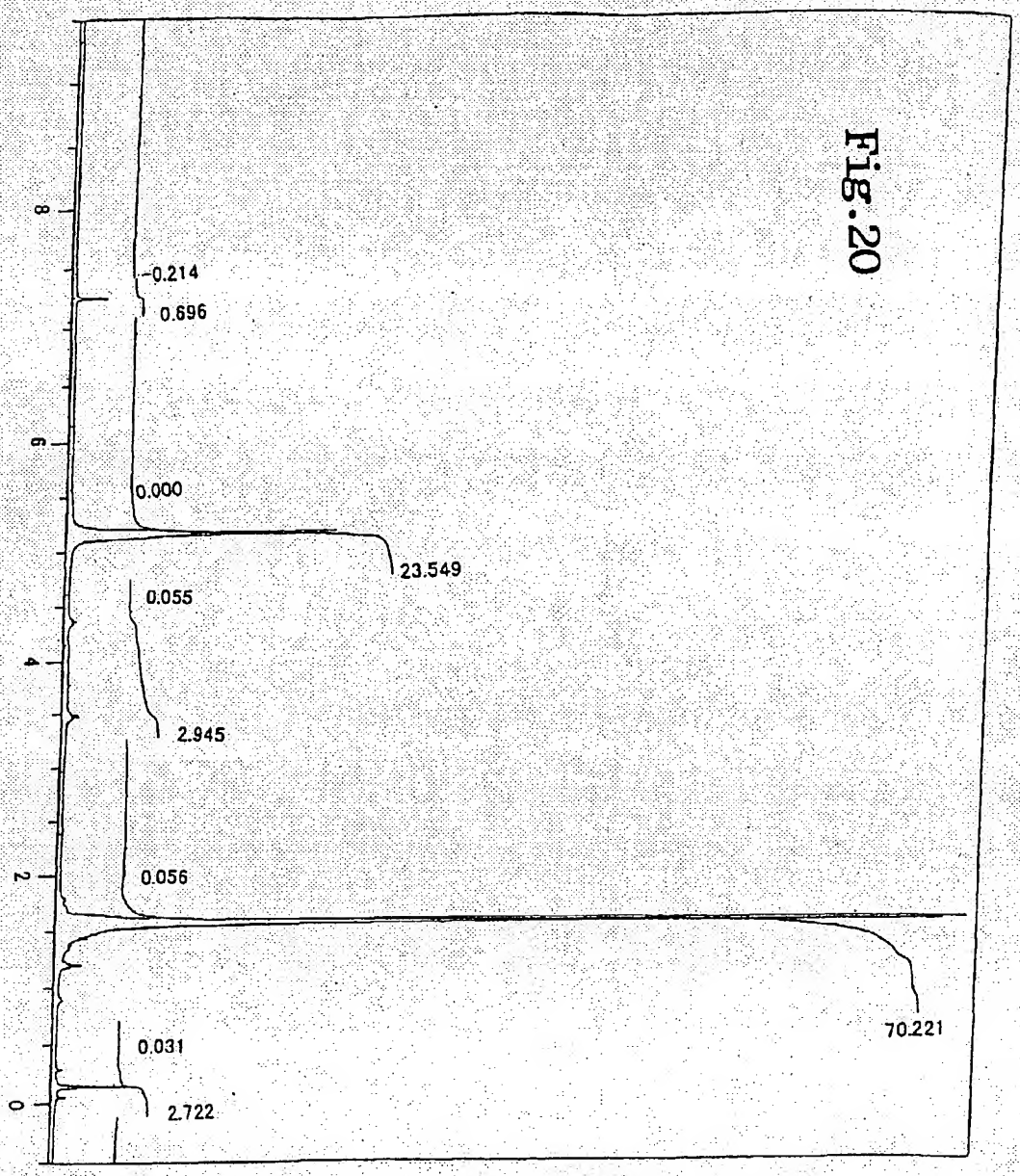


Fig.20

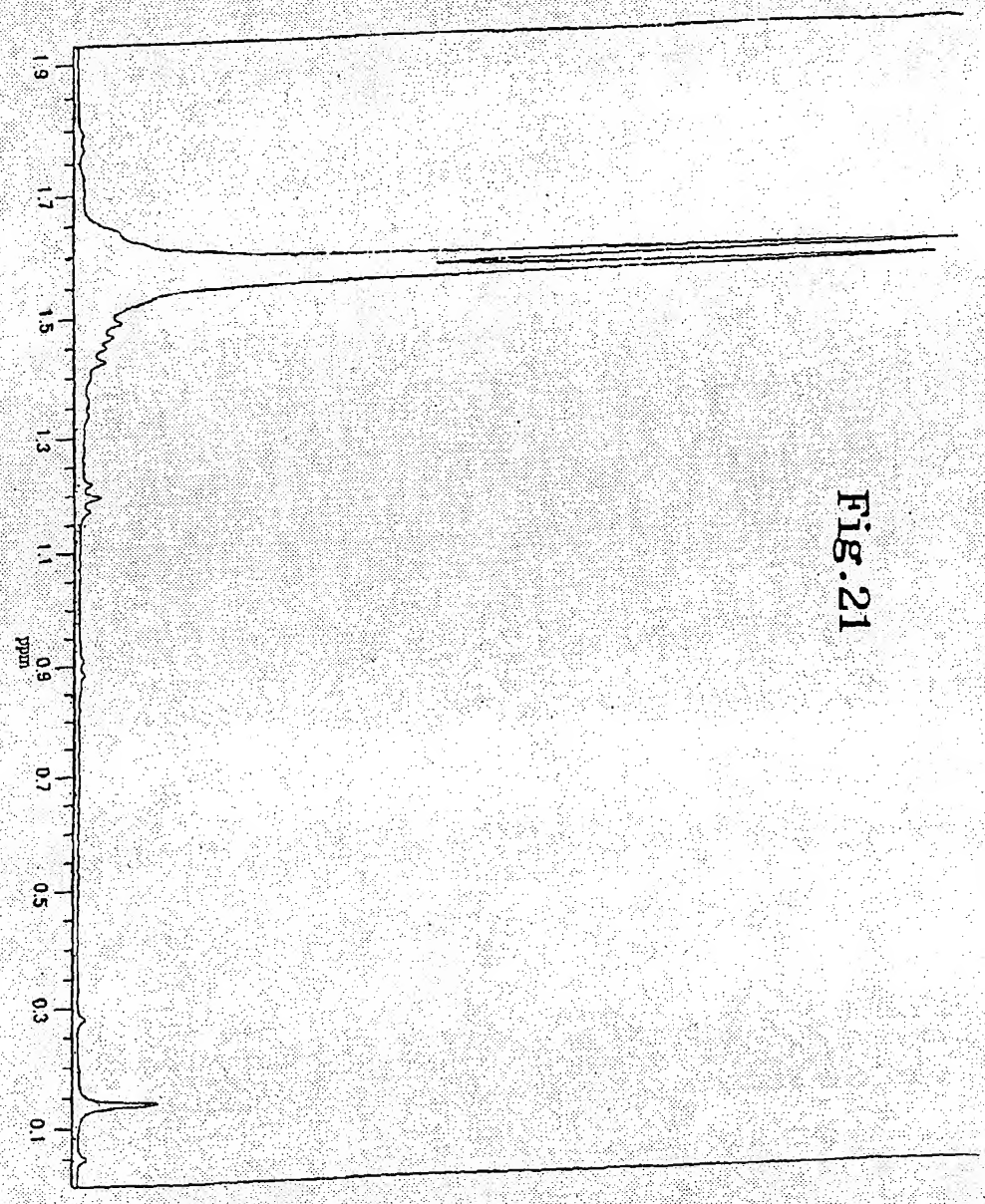


Fig.21

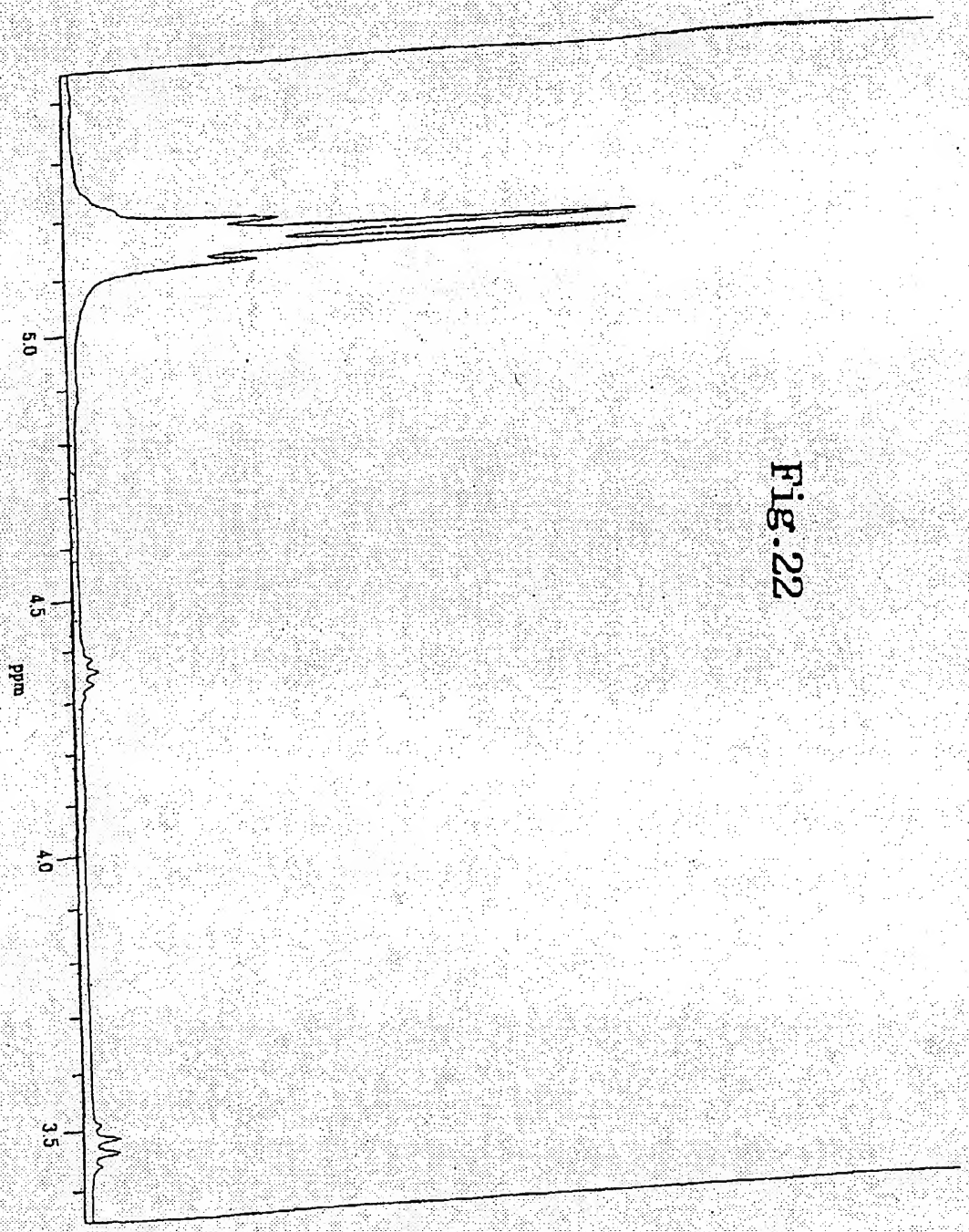


Fig. 22

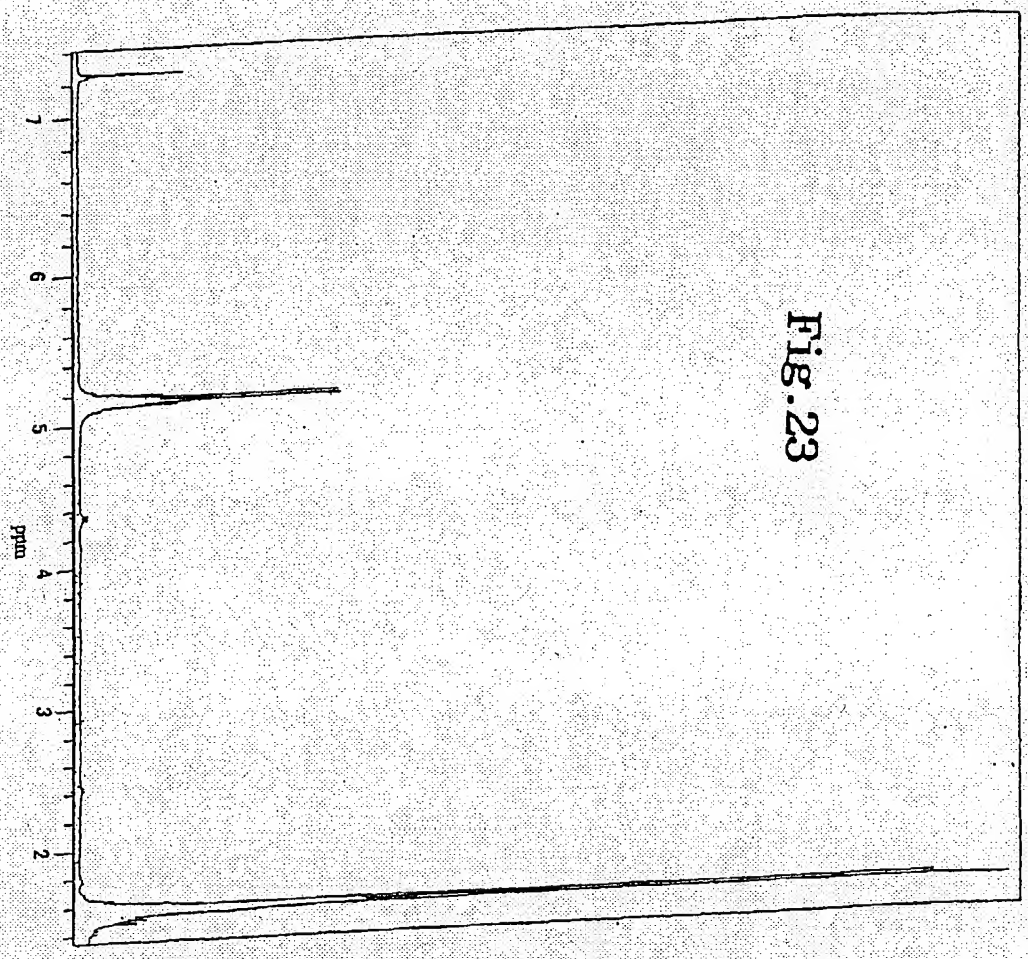


Fig.23

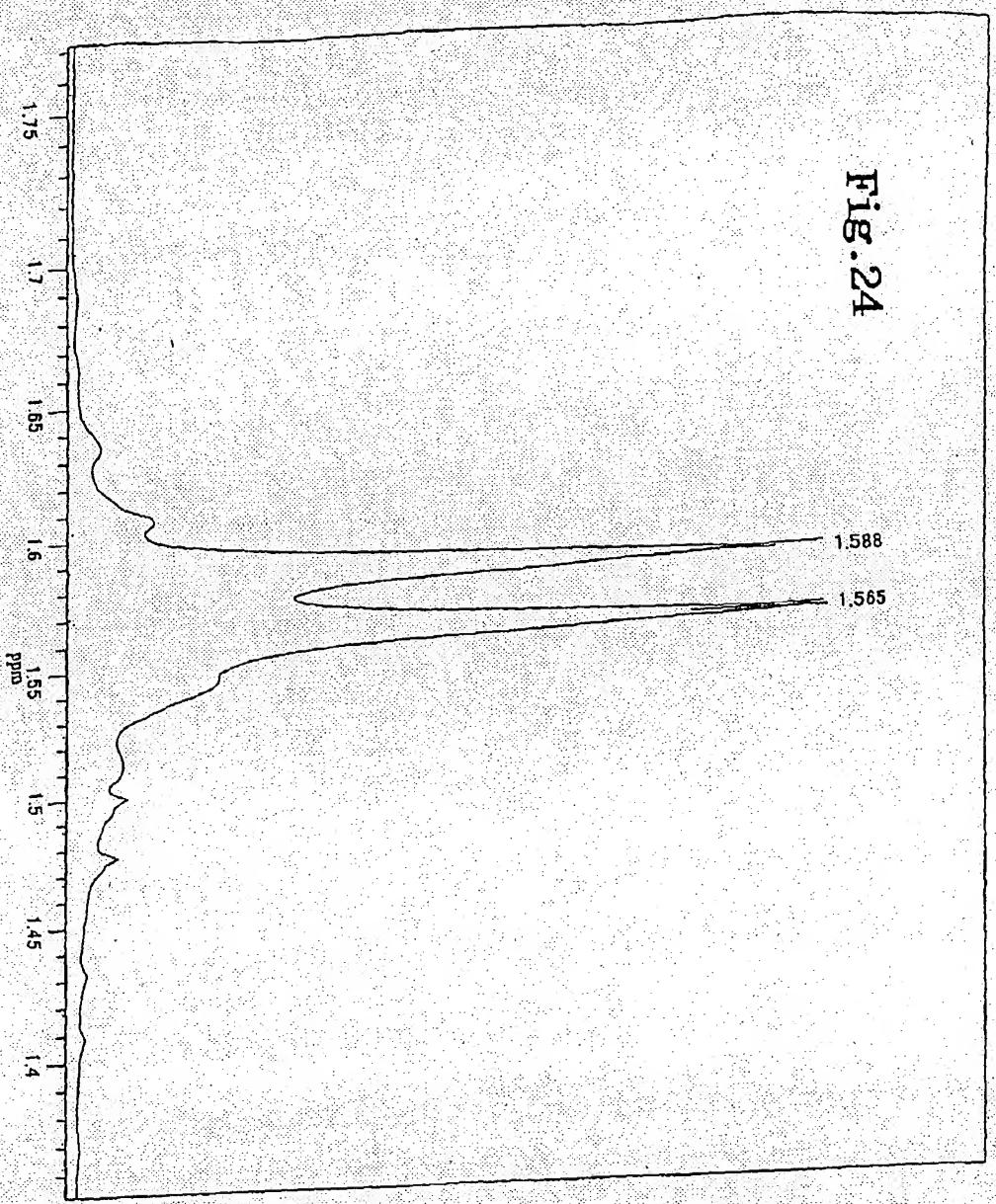


Fig.24

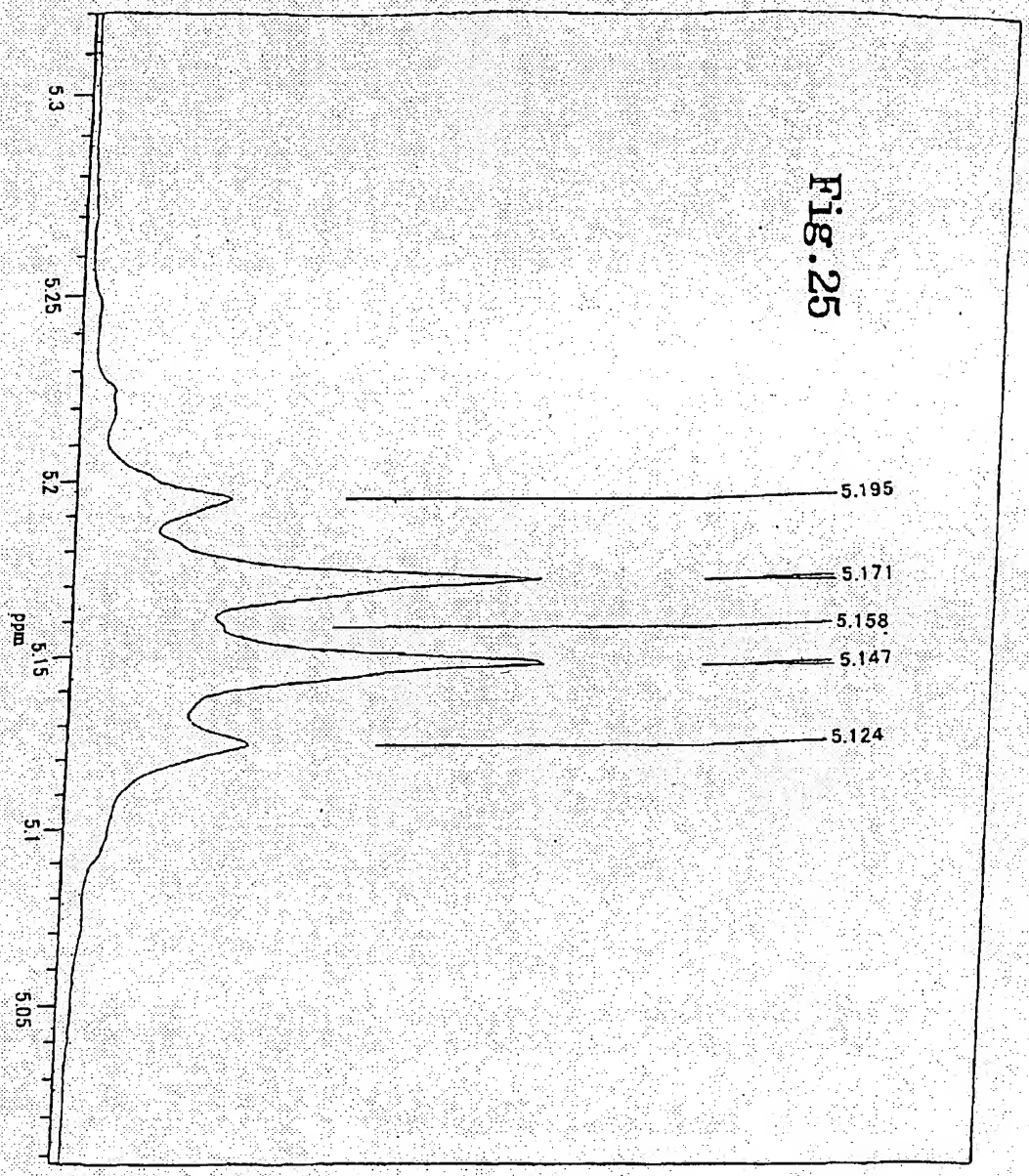


Fig.25

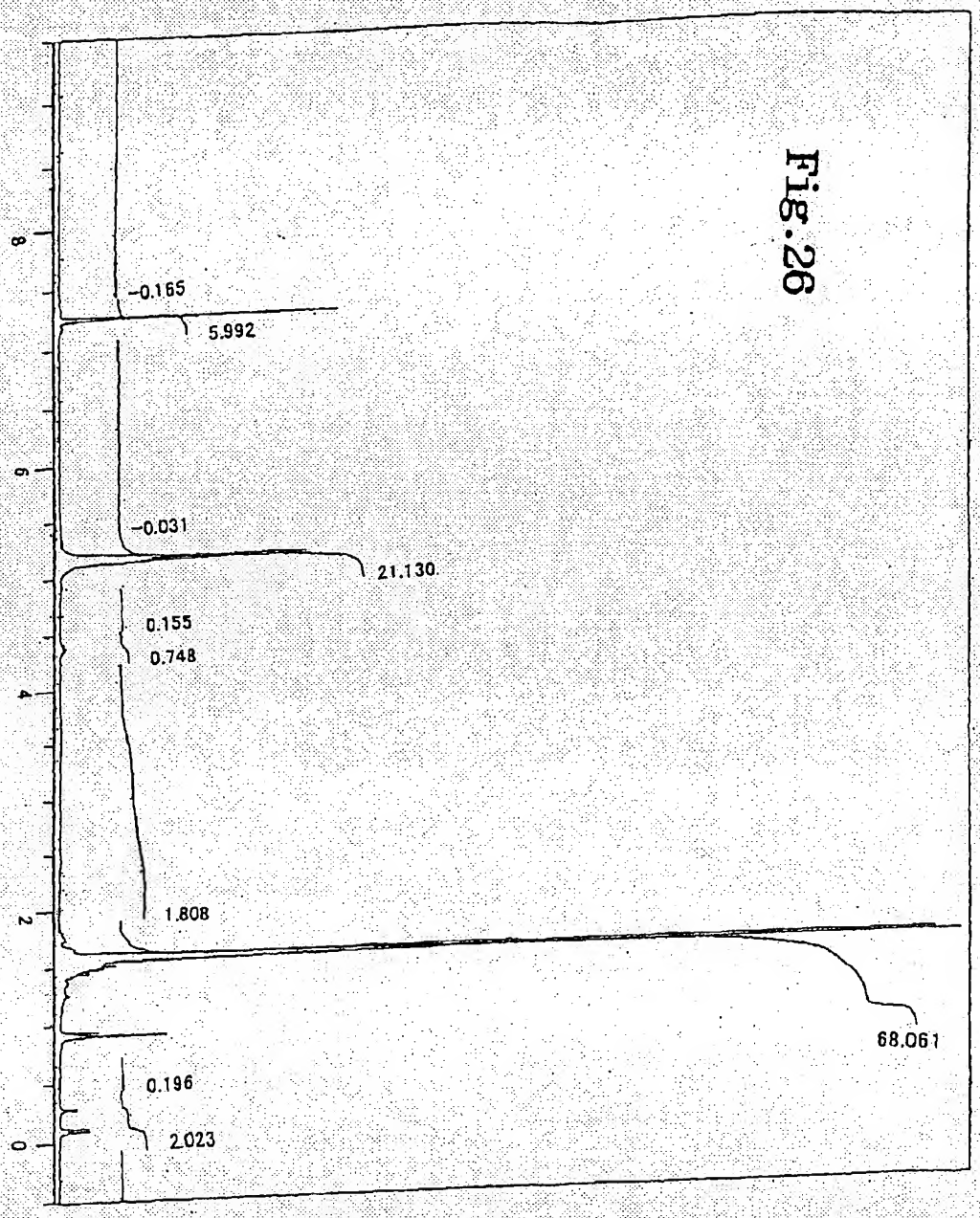


Fig.26

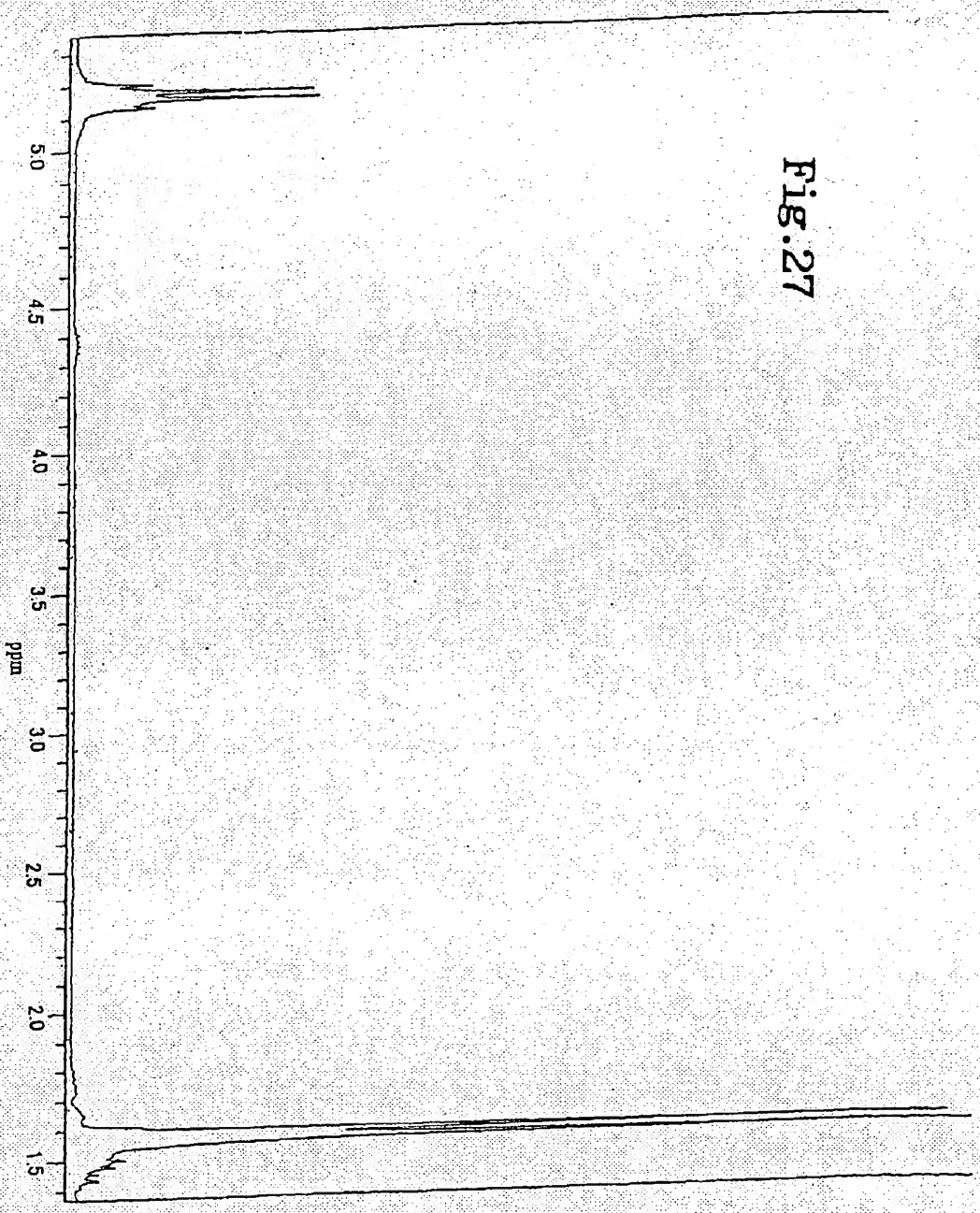
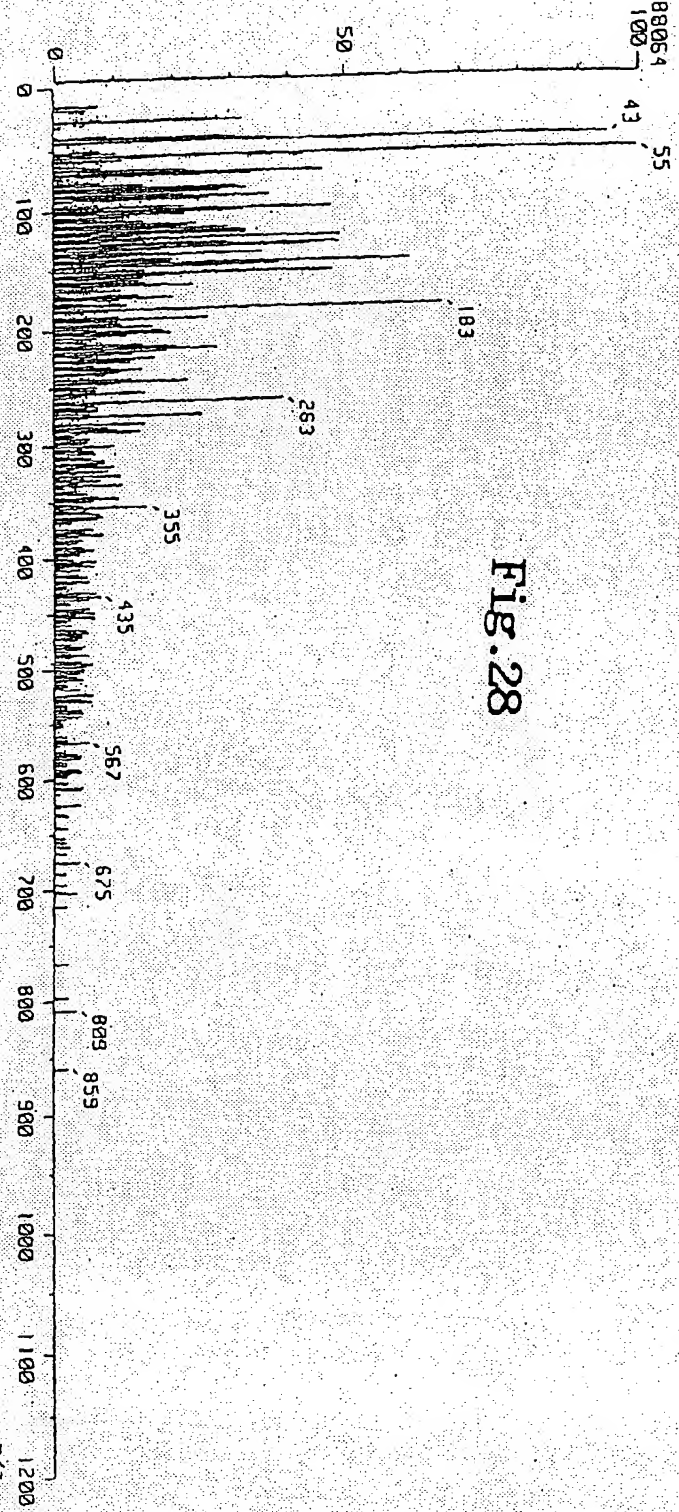


Fig.27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859
900
1000
1100
1200
m/z

Fig.28

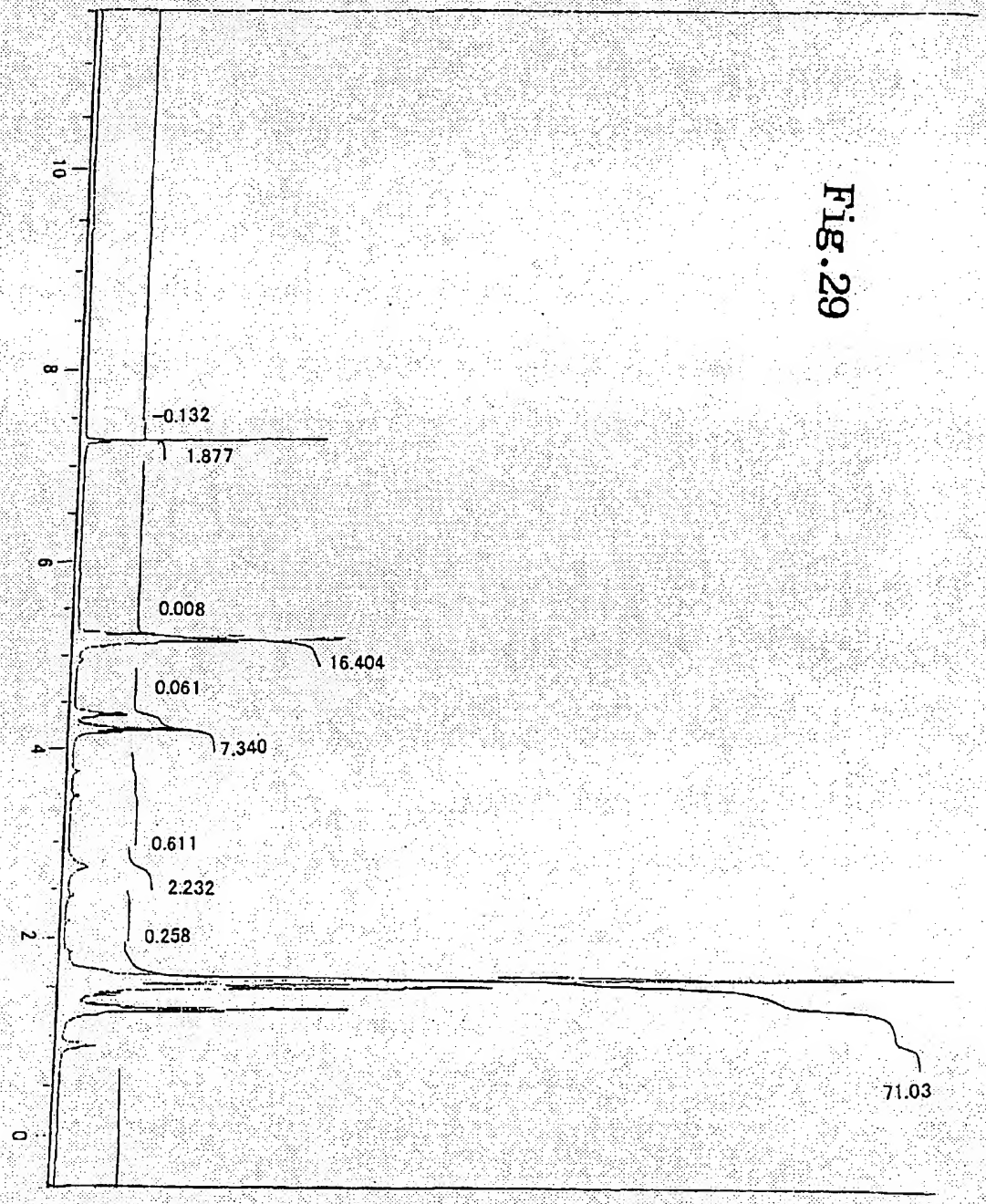
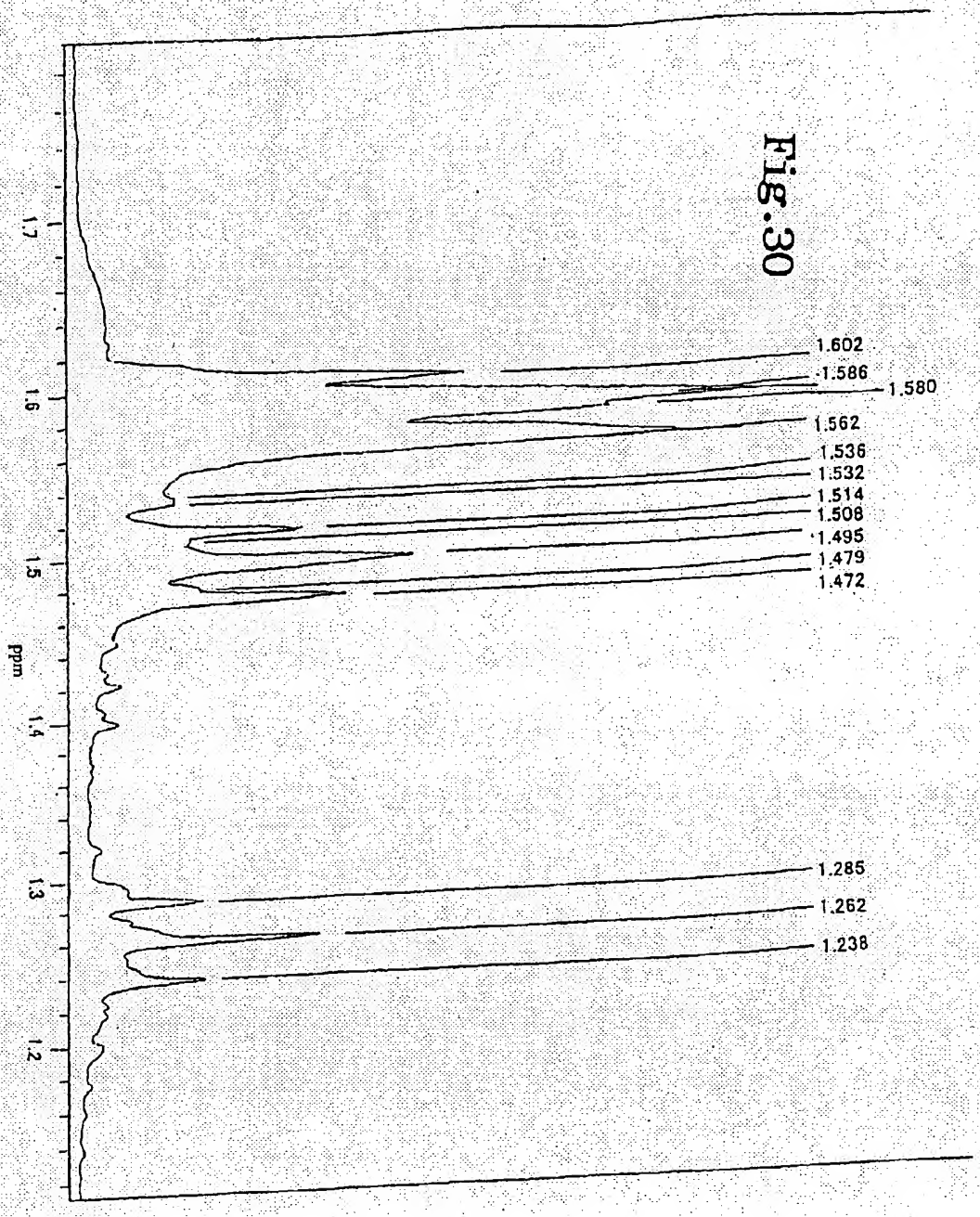


Fig.29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1.4
1.3
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ppm

Fig. 30

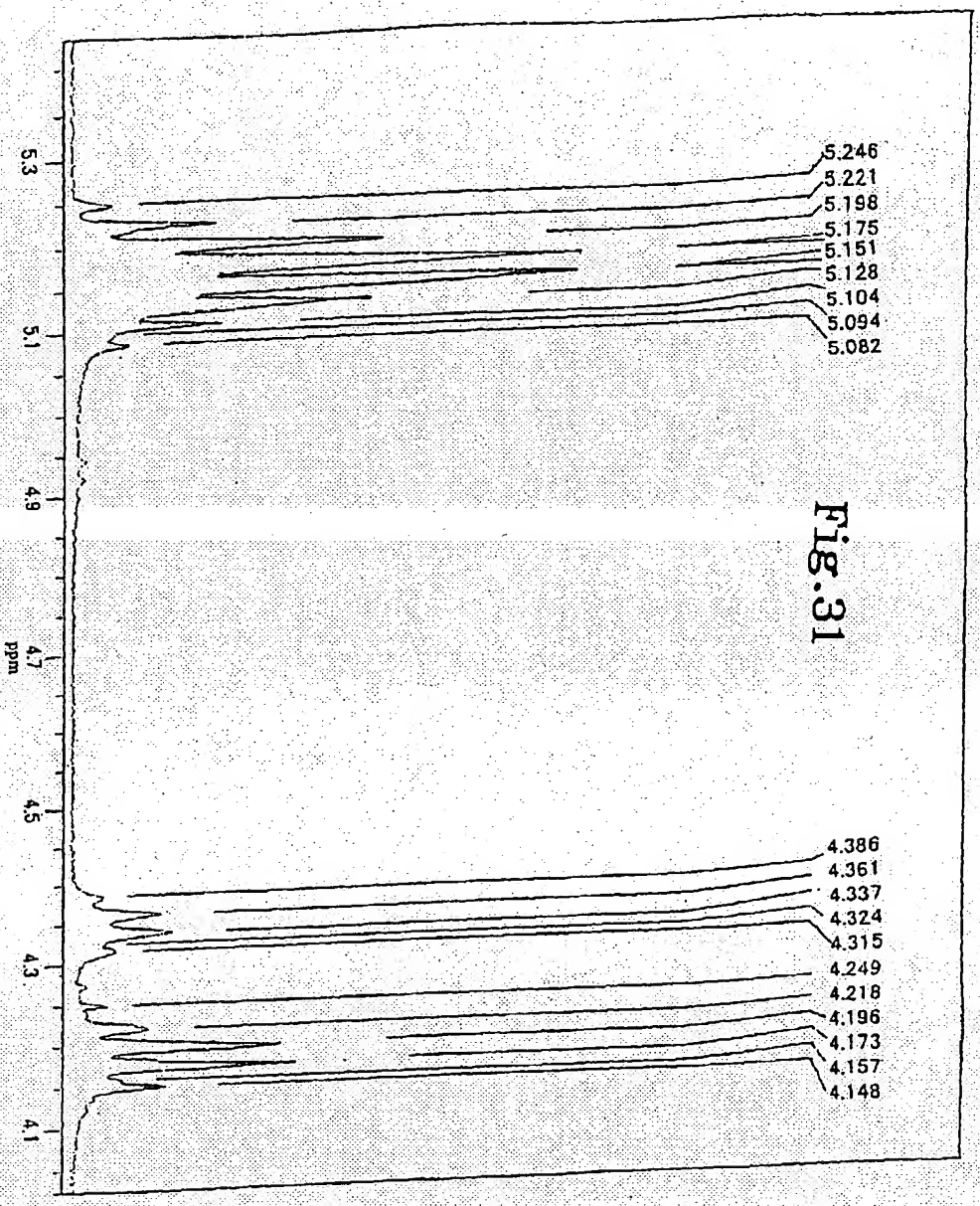
5.246
5.221
5.198
5.175
5.151
5.128
5.104
5.094
5.082
4.386
4.361
4.337
4.324
4.315
4.249
4.218
4.196
4.173
4.157
4.148
5.3
5.1
4.9
4.7
4.5
4.3
4.1
ppm

Fig.31

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP00/06398

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[7] C07D323/00 // C07D319/12, C07B61/00, A61K31/365, A61P35/00, 3/10, 3/04, 37/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[7] C07D323/00, C07D319/12

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAPLUS (STN), REGISTRY (STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Macromolecules (1988), 21(2), 286-93	1-9
Y	EP, 402676, A2 (GENERAL ELECTRIC COMPANY), 19 December, 1990 (12.19.90), especially, page 3, lines 23-28 & US, 5006637, A & JP, 3-74429, A	1-9
X	JP, 6-306264, A (Mitsui Toatsu Chemicals),	8-9
Y	01 November, 1994 (01.11.94), especially, Claim 4 (Family: none)	1-9

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 December, 2000 (19.12.00)	26 December, 2000 (26.12.00)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)